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(71) Applicant (for all designated States except US): SMITHKLINE BEECHAM CORPORATION [US/US]; One Franklin Plaza, Philadelphia, PA 19103 (US).**(72) Inventors; and****(75) Inventors/Applicants (for US only):** CALLAHAN, James, Francis [US/US]; 8214 Jeanes Street, Philadelphia, PA 19111 (US). COUSINS, Russell, Donovan [US/US]; 2053 Kings Row, Oxford, PA 19363 (US). KEENAN, Richard, McCulloch [US/US]; 796 Bass Cove, Malvern, PA 19355 (US). KWON, Chet [US/US]; Apartment 947, 3000 Valley Forge Circle, King of Prussia, PA 19406 (US). MILLER, William, Henry [US/US]; 333 Fell Lane, Schwenksville, PA 19473 (US). UZINKAS, Irene, Nijole [US/US]; 154 Vassar Circle, Villanova, PA 19085 (US).**(74) Agents:** McCARTHY, Mary, E. et al.; SmithKline Beecham Corporation, Corporate Intellectual Property UW2220, 709 Swedeland Road, P.O. Box 1539, King of Prussia, PA 19406-0939 (US).**(81) Designated States:** AL, AM, AU, BB, BG, BR, CA, CN, CZ, EE, GE, GH, HU, ID, IL, IS, JP, KG, KP, KR, LK, LR, LT, LV, MD, MG, MK, MN, MX, NO, NZ, PL, RO, SG, SI, SK, TR, TT, UA, US, UZ, VN, YU, ARIPO patent (GH, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).**Published***With international search report.***(54) Title:** VITRONECTIN RECEPTOR ANTAGONISTS**(57) Abstract**

Compounds having a benzodiazepinyl core structure are disclosed which are vitronectin receptor antagonists useful in the treatment of osteoporosis, angiogenesis, tumor growth and metastasis, atherosclerosis, restenosis and inflammation.

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TITLE

Vitronectin Receptor Antagonists

FIELD OF THE INVENTION

5 This invention relates to pharmaceutically active compounds which inhibit the vitronectin receptor and are useful for the treatment of inflammation, cancer and cardiovascular disorders, such as atherosclerosis and restenosis, and diseases wherein bone resorption is a factor, such as osteoporosis.

BACKGROUND OF THE INVENTION

10 Integrins are a superfamily of cell adhesion receptors, which are transmembrane glycoproteins expressed on a variety of cells. These cell surface adhesion receptors include gpIIb /IIIa (the fibrinogen receptor) and $\alpha_v\beta_3$ (the vitronectin receptor). The fibrinogen receptor gpIIb /IIIa is expressed on the platelet surface, and mediates platelet aggregation
15 and the formation of a hemostatic clot at the site of a bleeding wound. Philips, et al., *Blood.*, **1988**, 71, 831. The vitronectin receptor $\alpha_v\beta_3$ is expressed on a number of cells, including endothelial, smooth muscle, osteoclast, and tumor cells, and, thus, it has a variety of functions. The $\alpha_v\beta_3$ receptor expressed on the membrane of osteoclast cells mediates the adhesion of osteoclasts to the bone matrix, a key step in the bone resorption process. Ross,
20 et al., *J. Biol. Chem.*, **1987**, 262, 7703. A disease characterized by excessive bone resorption is osteoporosis. The $\alpha_v\beta_3$ receptor expressed on human aortic smooth muscle cells mediates their migration into neointima, a process which can lead to restenosis after percutaneous coronary angioplasty. Brown, et al., *Cardiovascular Res.*, **1994**, 28, 1815. Additionally, Brooks, et al., *Cell*, **1994**, 79, 1157 has shown that an $\alpha_v\beta_3$ antagonist is able
25 to promote tumor regression by inducing apoptosis of angiogenic blood vessels. Thus, agents that block the vitronectin receptor would be useful in treating diseases, such as osteoporosis, restenosis and cancer.

 The vitronectin receptor is now known to refer to three different integrins, designated $\alpha_v\beta_1$, $\alpha_v\beta_3$ and $\alpha_v\beta_5$. Horton, et al., *Int. J. Exp. Pathol.*, **1990**, 71, 741. $\alpha_v\beta_1$
30 binds fibronectin and vitronectin. $\alpha_v\beta_3$ binds a large variety of ligands, including fibrin, fibrinogen, laminin, thrombospondin, vitronectin, von Willebrand's factor, osteopontin and bone sialoprotein I. $\alpha_v\beta_5$ binds vitronectin. The vitronectin receptor $\alpha_v\beta_5$ has been shown to be involved in cell adhesion of a variety of cell types, including microvascular endothelial cells, (Davis, et al., *J. Cell. Biol.*, **1993**, 51, 206), and its role in angiogenesis
35 has been confirmed. Brooks, et al., *Science*, **1994**, 264, 569. This integrin is expressed on blood vessels in human wound granulation tissue, but not in normal skin.

The vitronectin receptor is known to bind to bone matrix proteins which contain the tri-peptide Arg-Gly-Asp (or RGD) motif. Thus, Horton, et al., *Exp. Cell Res.* **1991**, *195*, 368, disclose that RGD-containing peptides and an anti-vitronectin receptor antibody (23C6) inhibit dentine resorption and cell spreading by osteoclasts. In addition, Sato, et al.,
5 *J. Cell Biol.* **1990**, *111*, 1713 discloses that echistatin, a snake venom peptide which contains the RGD sequence, is a potent inhibitor of bone resorption in tissue culture, and inhibits attachment of osteoclasts to bone.

It has now been discovered that certain compounds are potent inhibitors of the $\alpha_v\beta_3$ and $\alpha_v\beta_5$ receptors. In particular, it has been discovered that such compounds are
10 more potent inhibitors of the vitronectin receptor than the fibrinogen receptor.

SUMMARY OF THE INVENTION

This invention comprises compounds of the formula (I) as described hereinafter, which have pharmacological activity for the inhibition of the vitronectin receptor and are
15 useful in the treatment of inflammation, cancer and cardiovascular disorders, such as atherosclerosis and restenosis, and diseases wherein bone resorption is a factor, such as osteoporosis.

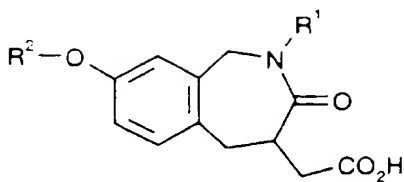
This invention is also a pharmaceutical composition comprising a compound according to formula (I) and a pharmaceutically carrier.

20 This invention is also a method of treating diseases which are mediated by the vitronectin receptor. In a particular aspect, the compounds of this invention are useful for treating atherosclerosis, restenosis, inflammation, cancer and diseases wherein bone resorption is a factor, such as osteoporosis.

DETAILED DESCRIPTION

25 This invention comprises novel compounds which are more potent inhibitors of the vitronectin receptor than the fibrinogen receptor. The novel compounds comprise a benzazepine core in which a nitrogen-containing substituent is present on the aromatic six-membered ring of the benzazepine and an aliphatic substituent containing an acidic moiety
30 is present on the seven-membered ring of the benzazepine. The benzazepine ring system is believed to interact favorably with the vitronectin receptor and to orient the substituent sidechains on the six and seven membered rings so that they may also interact favorably with the receptor. It is preferred that about twelve to fourteen intervening covalent bonds via the shortest intramolecular path will exist between the acidic group on the aliphatic
35 substituent of the seven-membered ring of the benzazepine and the nitrogen of the nitrogen-containing substituent on the aromatic six-membered ring of the benzazepine.

This invention comprises compounds of formula (I):



(I)

wherein:

5

R^1 is R^7 , or A- C_{0-4} alkyl, A- C_{2-4} alkenyl, A- C_{2-4} alkynyl, A- C_{3-4} oxoalkenyl, A- C_{3-4} oxoalkynyl, A- C_{1-4} aminoalkyl, A- C_{3-4} aminoalkenyl, A- C_{3-4} aminoalkynyl, optionally substituted by any accessible combination of one or more of R^{10} or R^7 ;

A is H, C_{3-6} cycloalkyl, Het or Ar;

10

R^7 is $-\text{COR}^8$, $-\text{COCR}'_2\text{R}^9$, $-\text{C(S)}\text{R}^8$, $-\text{S(O)}_m\text{OR}'$, $-\text{S(O)}_m\text{NR}'\text{R}''$, $-\text{PO(OR}')$, $-\text{PO(OR}')$, $-\text{NO}_2$, or tetrazolyl;

each R^8 independently is $-\text{OR}'$, $-\text{NR}'\text{R}''$, $-\text{NR}'\text{SO}_2\text{R}'$, $-\text{NR}'\text{OR}'$, or $-\text{OCR}'_2\text{CO(O)R}'$;

R^9 is $-\text{OR}'$, $-\text{CN}$, $-\text{S(O)}_r\text{R}'$, $-\text{S(O)}_m\text{NR}'_2$, $-\text{C(O)R}'$, $\text{C(O)NR}'_2$, or $-\text{CO}_2\text{R}'$;

R^{10} is H, halo, $-\text{OR}^{11}$, $-\text{CN}$, $-\text{NR}'\text{R}^{11}$, $-\text{NO}_2$, $-\text{CF}_3$, $\text{CF}_3\text{S(O)}_r$, $-\text{CO}_2\text{R}'$, $-\text{CONR}'_2$,

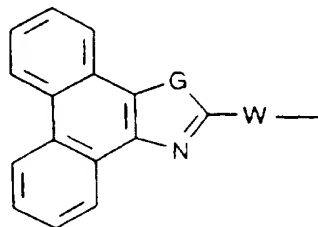
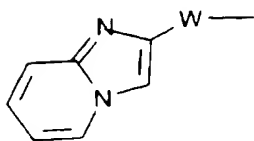
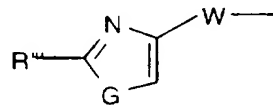
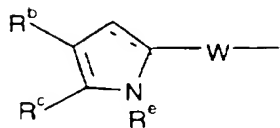
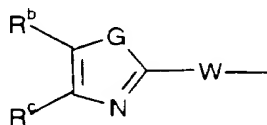
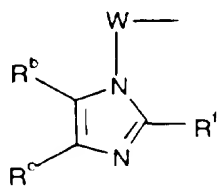
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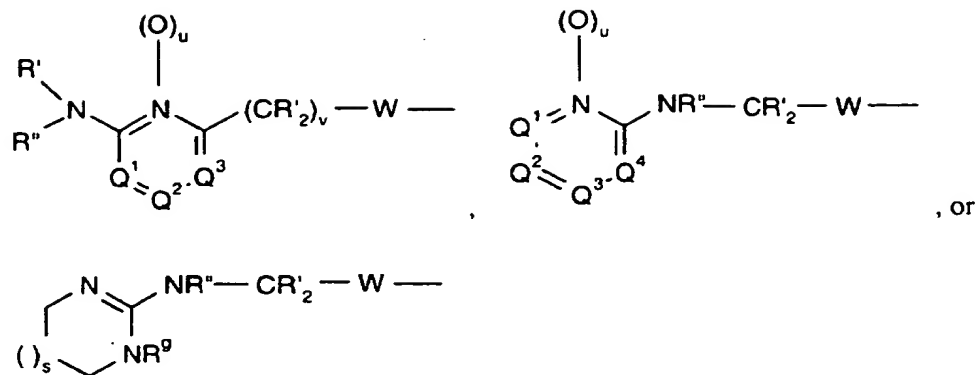
A- C_{0-6} alkyl-, A- C_{1-6} oxoalkyl-, A- C_{2-6} alkenyl-, A- C_{2-6} alkynyl-, A- C_{0-6} alkyloxy-, A- C_{0-6} alkylamino- or A- C_{0-6} alkyl-S(O) $_r$;

R^{11} is R' , $-\text{C(O)R}'$, $-\text{C(O)NR}'_2$, $-\text{C(O)OR}'$, $-\text{S(O)}_m\text{R}'$, or $-\text{S(O)}_m\text{NR}'_2$;

R^2 is

20





5

W is $-(\text{CHR}^g)_a\text{-U-}(\text{CHR}^g)_b\text{-}$;

U is absent or CO, CR^g₂, C(=CR^g₂), S(O)_k, O, NR^g, CR^gOR^g, CR^g(OR^k)CR^g₂, CR^g₂CR^g(OR^k), C(O)CR^g₂, CR^g₂C(O), CONRⁱ, NRⁱCO, OC(O), C(O)O, C(S)O, OC(S), C(S)NR^g, NR^gC(S), S(O)₂NR^g, NR^gS(O)₂, N=N, NR^gNR^g, NR^gCR^g₂, CR^g₂NR^g, CR^g₂O, OCR^g₂, C≡C or CR^g=CR^g;

G is NR^e, S or O;

R^g is H, C₁₋₆alkyl, Het-C₀₋₆alkyl, C₃₋₇cycloalkyl-C₀₋₆alkyl or Ar-C₀₋₆alkyl;

R^k is R^g, -C(O)R^g, or -C(O)OR^f;

Rⁱ is H, C₁₋₆alkyl, Het-C₀₋₆alkyl, C₃₋₇cycloalkyl-C₀₋₆alkyl, Ar-C₀₋₆alkyl, or C₁₋₆alkyl substituted by one to three groups chosen from halogen, CN, NR^g₂, OR^g, SR^g, CO₂R^g, and CON(R^g)₂;

R^f is H, C₁₋₆alkyl or Ar-C₀₋₆alkyl;

R^e is H, C₁₋₆alkyl, Ar-C₀₋₆alkyl, Het-C₀₋₆alkyl, C₃₋₇cycloalkyl-C₀₋₆alkyl, or (CH₂)_kCO₂R^g;

R^b and R^c are independently selected from H, C₁₋₆alkyl, Ar-C₀₋₆alkyl, Het-C₀₋₆alkyl, or C₃₋₆cycloalkyl-C₀₋₆alkyl, halogen, CF₃, OR^f, S(O)_kR^f, COR^f, NO₂, N(R^f)₂, CO(NR^f)₂, CH₂N(R^f)₂, or R^b and R^c are joined together to form a five or six membered aromatic or non-aromatic carbocyclic or heterocyclic ring, optionally substituted by up to three substituents chosen from halogen, CF₃, C₁₋₄alkyl, OR^f, S(O)_kR^f, COR^f, CO₂R^f, OH, NO₂, N(R^f)₂, CO(NR^f)₂, and CH₂N(R^f)₂; or methylenedioxy;

Q¹, Q², Q³ and Q⁴ are independently N or C-R^y, provided that no more than one of Q¹, Q², Q³ and Q⁴ is N;

R' is H, C₁₋₆alkyl, Ar-C₀₋₆alkyl or C₃₋₆cycloalkyl-C₀₋₆alkyl;

R'' is R', -C(O)R' or -C(O)OR';

R''' is H, C₁₋₆alkyl, Ar-C₀₋₆alkyl, Het-C₀₋₆alkyl, or C₃₋₆cycloalkyl-C₀₋₆alkyl, halogen, CF₃, OR^f, S(O)_kR^f, COR^f, NO₂, N(R^f)₂, CO(NR^f)₂, CH₂N(R^f)₂;

R^y is H, halo, -OR^E, -SR^E, -CN, -NR^ER^k, -NO₂, -CF₃, CF₃S(O)_r-, -CO₂R^E, -COR^E or -CONR^E₂, or C₁₋₆alkyl optionally substituted by halo, -OR^E, -SR^E, -CN, -NR^ER["], -NO₂, -CF₃, R'^S(O)_r-, -CO₂R^E, -COR^E or -CONR^E₂;

a is 0, 1 or 2;

5 b is 0, 1 or 2;

k is 0, 1 or 2;

m is 1 or 2;



r is 0, 1 or 2;

s is 0, 1 or 2;

10 u is 0 or 1; and

v is 0 or 1;

or a pharmaceutically acceptable salt thereof.

Also included in this invention are pharmaceutically acceptable addition salts and complexes of the compounds of this invention. In cases wherein the compounds of this invention may have one or more chiral centers, unless specified, this invention includes each unique nonracemic compound which may be synthesized and resolved by conventional techniques. In cases in which compounds have unsaturated carbon-carbon double bonds, both the cis (Z) and trans (E) isomers are within the scope of this invention. In cases wherein compounds may exist in tautomeric forms, such as keto-enol tautomers, such as  and , and each tautomeric form is contemplated as being included within this invention whether existing in equilibrium or locked in one form by appropriate substitution with R'.

The compounds of formula (I) inhibit the binding of vitronectin and other RGD-containing peptides to the vitronectin receptor. Inhibition of the vitronectin receptor on osteoclasts inhibits osteoclastic bone resorption and is useful in the treatment of diseases wherein bone resorption is associated with pathology, such as osteoporosis and osteoarthritis.

In another aspect, this invention is a method for stimulating bone formation which comprises administering a compound which causes an increase in osteocalcin release. Increased bone production is a clear benefit in disease states wherein there is a deficiency of mineralized bone mass or remodeling of bone is desired, such as fracture healing and the prevention of bone fractures. Diseases and metabolic disorders which result in loss of bone structure would also benefit from such treatment. For instance, hyperparathyroidism, Paget's disease, hypercalcemia of malignancy, osteolytic lesions produced by bone metastasis, bone loss due to immobilization or sex hormone deficiency, Behçet's disease,

osteomalacia, hyperostosis and osteopetrosis, could benefit from administering a compound of this invention.

Additionally, since the compounds of the instant invention inhibit vitronectin receptors on a number of different types of cells, said compounds would be useful in the treatment of inflammatory disorders, such as rheumatoid arthritis and psoriasis, and cardiovascular diseases, such as atherosclerosis and restenosis. The compounds of Formula (I) of the present invention may be useful for the treatment or prevention of other diseases including, but not limited to, thromboembolic disorders, asthma, allergies, adult respiratory distress syndrome, graft versus host disease, organ transplant rejection, septic shock, eczema, contact dermatitis, inflammatory bowel disease, and other autoimmune diseases. The compounds of the present invention may also be useful for wound healing.

The compounds of the present invention are also useful for the treatment, including prevention, of angiogenic disorders. The term angiogenic disorders as used herein includes conditions involving abnormal neovascularization. Where the growth of new blood vessels is the cause of, or contributes to, the pathology associated with a disease, inhibition of angiogenesis will reduce the deleterious effects of the disease. An example of such a disease target is diabetic retinopathy. Where the growth of new blood vessels is required to support growth of a deleterious tissue, inhibition of angiogenesis will reduce the blood supply to the tissue and thereby contribute to reduction in tissue mass based on blood supply requirements. Examples include growth of tumors where neovascularization is a continual requirement in order that the tumor grow and the establishment of solid tumor metastases. Thus, the compounds of the present invention inhibit tumor tissue angiogenesis, thereby preventing tumor metastasis and tumor growth.

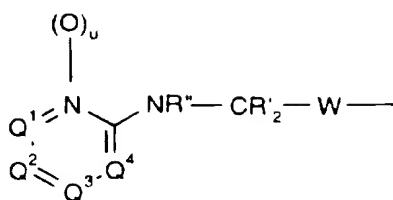
Thus, according to the methods of the present invention, the inhibition of angiogenesis using the compounds of the present invention can ameliorate the symptoms of the disease, and, in some cases, can cure the disease.

Another therapeutic target for the compounds of the instant invention are eye diseases characterized by neovascularization. Such eye diseases include corneal neovascular disorders, such as corneal transplantation, herpetic keratitis, luetic keratitis, pterygium and neovascular pannus associated with contact lens use. Additional eye diseases also include age-related macular degeneration, presumed ocular histoplasmosis, retinopathy of prematurity and neovascular glaucoma.

This invention further provides a method of inhibiting tumor growth which comprises administering stepwise or in physical combination a compound of formula (I) and an antineoplastic agent, such as topotecan and cisplatin.

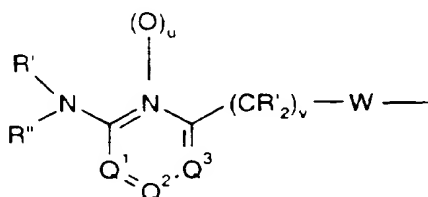
With respect to formula (I):

Suitably R^2 is



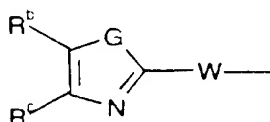
- 5 , wherein Q^1 , Q^2 , and Q^3 are each CR^Y , Q^4 is CR^Y or N and u is 0, and preferably, each R' is H, R'' is H, C_{1-6} alkyl, $-C(O)C_{1-6}$ alkyl, $C(O)OC_{1-6}$ alkyl, $-C(O)C_{0-6}$ alkyl-Ar, or $C(O)OC_{0-6}$ alkyl-Ar, W is $-CH_2-CH_2-$, and R^Y is H, halo, $-OR^E$, $-SR^E$, $-CN$, $-NR^E R^K$, $-NO_2$, $-CF_3$, $CF_3S(O)_r$, $-CO_2R^E$, $-COR^E$, $-CONR^E_2$, or C_{1-6} alkyl.

Alternately R^2 is



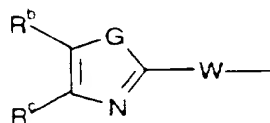
- 10 , wherein Q^1 , Q^2 , and Q^3 are each CH and u is 0, and preferably, each R' is H, R'' is H or C_{1-4} alkyl, W is $-CH_2-CH_2-$ and v is 0.

Alternately R^2 is



- 15 , wherein G is NH and R^b and R^c are each H, and preferably, W is $-NR^E-(CHR^E)_b-$.

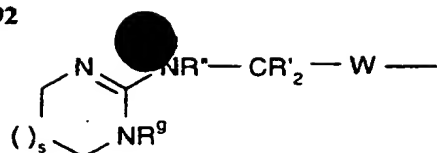
Alternately R^2 is



- 20 , wherein G is NH and R^b and R^c are joined together to form a five or six membered aromatic or non-aromatic carbocyclic or heterocyclic ring, optionally substituted by up to three substituents chosen from halogen, CF_3 , C_{1-4} alkyl, OR^f , $S(O)_kR^f$, COR^f , CO_2R^f , OH, NO_2 , $N(R^f)_2$, $CO(NR^f)_2$, and $CH_2N(R^f)_2$; or methylenedioxy. Preferably, R^b and R^c are joined together to form a six membered aromatic carbocyclic or heterocyclic ring and W is $-CH_2-CH_2-$.

Alternately R^2 is

25



, wherein each R' is H, R'' is H or C₁₋₄alkyl,

R⁸ is H or C₁₋₄alkyl and s is 0, 1 or 2 and, preferably, W is -CH₂-CH₂-.

With respect to formula (I), suitably R¹ is H, C₁₋₆alkyl, Ar-C₀₋₆alkyl, Het-C₀₋₆alkyl, C₃₋₆cycloalkyl-C₀₋₆alkyl, -CH₂CF₃, -(CH₂)₁₋₂C(O)OR', or -(CH₂)₂OR'.

- 5 Preferably, R¹ is H, C₁₋₄alkyl, Ph-C₀₋₄alkyl, -CH₂CF₃, -(CH₂)₁₋₂C(O)OR', or -(CH₂)₂OR', in which R' is H or C₁₋₄alkyl. Most preferably, R¹ is -CH₂CF₃.

Representative of the novel compounds of this invention are the following:

- (±)-8-[3-(2-pyridylamino)-1-propyloxy]-3-oxo-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetic acid;
- 10 (±)-8-[3-(4-amino-2-pyridylamino)-1-propyloxy]-3-oxo-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetic acid;
- (±)-8-[3-(4-methoxy-2-pyridylamino)-1-propyloxy]-3-oxo-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetic acid;
- (±)-8-[3-(2-pyridylamino)-1-propyloxy]-2-methyl-3-oxo-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetic acid;
- 15 (±)-8-[3-(2-imidazolylamino)-1-propyloxy]-3-oxo-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetic acid;
- (±)-8-[3-[2-(1,4,5,6-tetrahydropyrimidinyl)amino]-1-propyloxy]-3-oxo-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetic acid;
- 20 (±)-8-[2-[6-(methylamino)pyridyl]ethoxy]-3-oxo-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetic acid;
- (±)-8-[2-(2-benzimidazolyl)ethoxy]-3-oxo-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetic acid;
- (±)-8-[2-(4-aza-2-benzimidazolyl)ethoxy]-3-oxo-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetic acid;
- 25 (±)-8-[2-[6-(methylamino)pyridin-2-yl]-1-ethoxy]-3-oxo-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetic acid;
- (±)-8-[2-(benzimidazol-2-yl)-1-ethoxy]-3-oxo-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetic acid;
- 30 (±)-8-[3-(4-aminopyridin-2-ylamino)-1-propyloxy]-2-methyl-3-oxo-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetic acid;
- (±)-3-oxo-8-[3-(pyrimidin-2-ylamino)-1-propyloxy]-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetic acid;
- (R)-8-[3-(4-aminopyridin-2-ylamino)-1-propyloxy]-3-oxo-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetic acid;
- 35

- (±)-3-oxo-8-[3-[(1,4,5,6-tetrahydropyrimidin-2-yl)amino]-1-propyloxy]-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetic acid;
- (S)-8-[3-(4-aminopyridin-2-ylamino)-1-propyloxy]-3-oxo-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetic acid;
- 5 (±)-3-oxo-8-[3-[N-(pyridin-2-yl)-N-(*tert*-butoxycarbonyl)amino]-1-propyloxy]-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetic acid;
- (±)-8-[3-[N-(1-oxopyridin-2-yl)-N-(*tert*-butoxycarbonyl)amino]-1-propyloxy]-3-oxo-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetic acid;
- (±)-3-oxo-8-[3-[N-(pyridin-2-yl)-N-(*tert*-butoxycarbonyl)amino]-1-propyloxy]-2-(4-trifluoromethylbenzyl)-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetic acid;
- 10 (±)-3-oxo-8-[3-(pyridin-2-ylamino)-1-propyloxy]-2-(4-trifluoromethylbenzyl)-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetic acid;
- (±)-2-methyl-3-oxo-8-[3-[N-(pyridin-2-yl)-N-(methyl)amino]-1-propyloxy]-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetic acid;
- 15 (±)-2-benzyl-3-oxo-8-[3-(pyridin-2-ylamino)-1-propyloxy]-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetic acid;
- (±)-2-(carboxymethyl)-3-oxo-8-[3-(pyridin-2-ylamino)-1-propyloxy]-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetic acid;
- (±)-2-(4-aminobenzyl)-3-oxo-8-[3-(pyridin-2-ylamino)-1-propyloxy]-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetic acid;
- 20 (±)-3-oxo-8-[3-[N-(pyridin-2-yl)-N-(benzoyl)amino]-1-propyloxy]-2-(4-trifluoromethylbenzyl)-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetic acid;
- (±)-8-[3-(2-imidazolin-2-ylamino)-1-propyloxy]-2-methyl-3-oxo-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetic acid;
- 25 (±)-3-oxo-8-[3-(pyridin-2-ylamino)-1-propyloxy]-2-(2,2,2-trifluoroethyl)-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetic acid;
- (±)-8-[2-(2-aminothiazol-4-yl)-1-ethoxy]-2-methyl-3-oxo-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetic acid;
- (±)-8-[3-(4,6-dimethylpyridin-2-ylamino)-1-propyloxy]-2-methyl-3-oxo-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetic acid;
- 30 (±)-8-[3-(4,5,6,7-tetrahydro-1H-1,3-diazepin-2-ylamino)-1-propyloxy]-2-methyl-3-oxo-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetic acid;
- (±)-3-oxo-8-[3-[N-(pyridin-2-yl)-N-(*tert*-butylacetyl)amino]-1-propyloxy]-2-(4-trifluoromethylbenzyl)-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetic acid;
- 35 (±)-3-oxo-8-[3-[N-(pyridin-2-yl)-N-(isobutoxycarbonyl)amino]-1-propyloxy]-2-(4-trifluoromethylbenzyl)-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetic acid;

(S)-3-oxo-8-[3-(pyridin-2-ylamino)-1-propyloxy]-2-(4-trifluoromethylbenzyl)-
2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetic acid;

(±)-3-oxo-8-[3-(4-methylpyridin-2-ylamino)-1-propyloxy]-2-(2,2,2-trifluoroethyl)-
2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetic acid;

5 (±)-3-oxo-8-[3-[N-(pyridin-2-yl)-N-(methylamino)]-1-propyloxy]-2-[4-
(trifluoromethyl)benzyl]-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetic acid;

(S)-3-oxo-8-[3-(pyridin-2-ylamino)-1-propyloxy]-2-(2,2,2-trifluoroethyl)-2,3,4,5-
tetrahydro-1H-2-benzazepine-4-acetic acid;

10 (R)-3-oxo-8-[3-(pyridin-2-ylamino)-1-propyloxy]-2-(2,2,2-trifluoroethyl)-2,3,4,5-
tetrahydro-1H-2-benzazepine-4-acetic acid;

(S)-8-[3-(4-methylpyridin-2-ylamino)-1-propyloxy]-3-oxo-2-(2,2,2-trifluoroethyl)-
2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetic acid;

(S)-3-oxo-8-[3-(1,4,5,6-tetrahydropyrimid-2-ylamino)-1-propyloxy]-2-[4-
(trifluoromethyl)benzyl]-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetic acid;

15 (S)-3-oxo-2-(2-phenylethyl)-8-[3-(pyridin-2-ylamino)-1-propyloxy]-2,3,4,5-
tetrahydro-1H-2-benzazepine-4-acetic acid;

(S)-8-[2-[6-(methylamino)pyridin-2-yl]-1-ethoxy]-3-oxo-2-(2-phenylethyl)-2,3,4,5-
tetrahydro-1H-2-benzazepine-4-acetic acid;

20 (S)-8-[2-[6-(methylamino)pyridin-2-yl]-1-ethoxy]-3-oxo-2-(2,2,2-trifluoroethyl)-
2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetic acid; and

(S)-8-[2-[6-(methylamino)pyridin-2-yl]-1-ethoxy]-3-oxo-2-[4-
(trifluoromethyl)benzyl]-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetic acid;

or a pharmaceutically acceptable salt thereof.

Preferred compounds of this invention include:

25 (S)-3-oxo-8-[3-(pyridin-2-ylamino)-1-propyloxy]-2-(2,2,2-trifluoroethyl)-2,3,4,5-
tetrahydro-1H-2-benzazepine-4-acetic acid;

(S)-8-[2-[6-(methylamino)pyridin-2-yl]-1-ethoxy]-3-oxo-2-(2,2,2-trifluoroethyl)-
2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetic acid; and

30 (S)-8-[3-(4-methylpyridin-2-ylamino)-1-propyloxy]-3-oxo-2-(2,2,2-trifluoroethyl)-
2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetic acid;

or a pharmaceutically acceptable salt thereof.

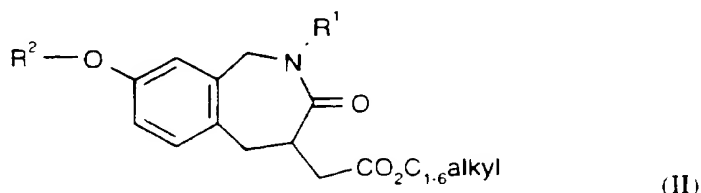
In cases wherein the compounds of this invention may have one or more chiral
centers, unless specified, this invention includes each unique nonracemic compound which
may be synthesized and resolved by conventional techniques. According to the present
35 invention, the (S) configuration of the formula (I) compounds is preferred.

In cases in which compounds have unsaturated carbon-carbon double bonds, both
the cis (Z) and trans (E) isomers are within the scope of this invention. The meaning of any

substituent at any one occurrence is independent of its meaning, or any other substituent's meaning, at any other occurrence.

Also included in this invention are prodrugs of the compounds of this invention.

- Prodrugs are considered to be any covalently bonded carriers which release the active parent drug according to formula (I) *in vivo*. Thus, in another aspect of this invention are novel prodrugs, which are also intermediates in the preparation of formula (I) compounds, of formula (II):



10

wherein:

- R^1 is R^7 , or A-C₀₋₄alkyl, A-C₂₋₄alkenyl, A-C₂₋₄alkynyl, A-C₃₋₄oxoalkenyl, A-C₃₋₄oxoalkynyl, A-C₁₋₄aminoalkyl, A-C₃₋₄aminoalkenyl, A-C₃₋₄aminoalkynyl, optionally substituted by any accessible combination of one or more of R^{10} or R^7 ;

A is H, C₃₋₆cycloalkyl, Het or Ar;

R^7 is -COR⁸, -COCR⁹, -C(S)R⁸, -S(O)_mOR', -S(O)_mNR'R'', -PO(OR'), -PO(OR')₂, -NO₂, or tetrazolyl;

each R^8 independently is -OR', -NR'R'', -NR'SO₂K', -NR'OR', or -OCR'₂CO(O)R';

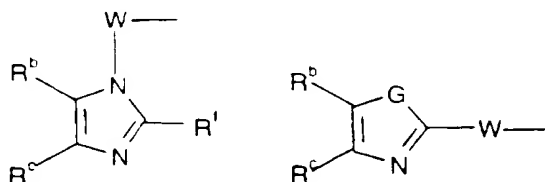
- R^9 is -OR', -CN, -S(O)_rR', -S(O)_mNR'₂, -C(O)R', C(O)NR'₂, or -CO₂R';

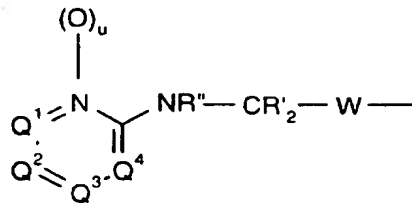
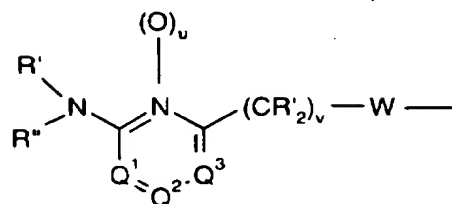
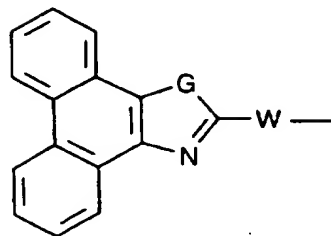
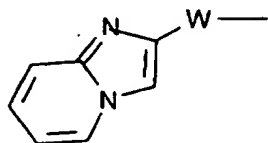
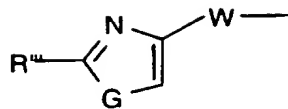
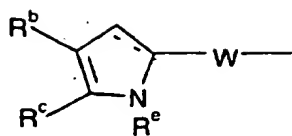
R^{10} is H, halo, -OR¹¹, -CN, -NR'R¹¹, -NO₂, -CF₃, CF₃S(O)_r-, -CO₂R', -CONR'₂, A-C₀₋₆alkyl-, A-C₁₋₆oxoalkyl-, A-C₂₋₆alkenyl-, A-C₂₋₆alkynyl-, A-C₀₋₆alkyloxy-, A-C₀₋₆alkylamino- or A-C₀₋₆alkyl-S(O)_r;

R^{11} is R', -C(O)R', -C(O)NR'₂, -C(O)OR', -S(O)_mR', or -S(O)_mNR'₂;

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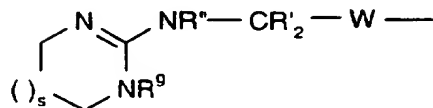
R^2 is





5

, or



W is $-(\text{CHR}^g)_a\text{-U-}(\text{CHR}^g)_b\text{-}$;

10

U is absent or CO, CR^g_2 , $\text{C(=CR}^g_2\text{)}$, S(O)_k , O, NR^g , CR^gOR^g , $\text{CR}^g(\text{OR}^k)\text{CR}^g_2$, $\text{CR}^g_2\text{CR}^g(\text{OR}^k)$, C(O)CR^g_2 , $\text{CR}^g_2\text{C(O)}$, CONR^i , NR^iCO , OC(O) , C(O)O , C(S)O , OC(S) , C(S)NR^g , $\text{NR}^g\text{C(S)}$, $\text{S(O)}_2\text{NR}^g$, $\text{NR}^g\text{S(O)}_2$, N=N , NR^gNR^g , NR^gCR^g_2 , CR^g_2NR^g , CR^g_2O , OCR^g_2 , $\text{C}\equiv\text{C}$ or $\text{CR}^g=\text{CR}^g$;

G is NR^c , S or O;

15

R^g is H, $\text{C}_{1-6}\text{alkyl}$, $\text{Het-C}_{0-6}\text{alkyl}$, $\text{C}_{3-7}\text{cycloalkyl-C}_{0-6}\text{alkyl}$ or $\text{Ar-C}_{0-6}\text{alkyl}$;

R^k is R^g , $-\text{C(O)R}^g$, or $-\text{C(O)OR}^f$;

R^i is H, $\text{C}_{1-6}\text{alkyl}$, $\text{Het-C}_{0-6}\text{alkyl}$, $\text{C}_{3-7}\text{cycloalkyl-C}_{0-6}\text{alkyl}$, $\text{Ar-C}_{0-6}\text{alkyl}$, or $\text{C}_{1-6}\text{alkyl}$ substituted by one to three groups chosen from halogen, CN, NR^g_2 , OR^g , SR^g , CO_2R^g , and $\text{CON(R}^g)_2$;

20

R^f is H, $\text{C}_{1-6}\text{alkyl}$ or $\text{Ar-C}_{0-6}\text{alkyl}$;

R^e is H, $\text{C}_{1-6}\text{alkyl}$, $\text{Ar-C}_{0-6}\text{alkyl}$, $\text{Het-C}_{0-6}\text{alkyl}$, $\text{C}_{3-7}\text{cycloalkyl-C}_{0-6}\text{alkyl}$, or $(\text{CH}_2)_k\text{CO}_2\text{R}^g$;

R^b and R^c are independently selected from H, $\text{C}_{1-6}\text{alkyl}$, $\text{Ar-C}_{0-6}\text{alkyl}$, $\text{Het-C}_{0-6}\text{alkyl}$, or $\text{C}_{3-6}\text{cycloalkyl-C}_{0-6}\text{alkyl}$, halogen, CF_3 , OR^f , $\text{S(O)}_k\text{R}^f$, COR^f , NO_2 , $\text{N(R}^f)_2$,

CO(NR^f)₂, CH₂N(R^f)₂, or R^b and R^c are joined together to form a five or six membered aromatic or non-aromatic carbocyclic or heterocyclic ring, optionally substituted by up to three substituents chosen from halogen, CF₃, C₁₋₄alkyl, OR^f, S(O)_kR^f, COR^f, CO₂R^f, OH, NO₂, N(R^f)₂, CO(NR^f)₂, and CH₂N(R^f)₂; or methylenedioxy;

5 Q¹, Q², Q³ and Q⁴ are independently N or C-R^y, provided that no more than one of Q¹, Q², Q³ and Q⁴ is N;

R' is H, C₁₋₆alkyl, Ar-C₀₋₆alkyl or C₃₋₆cycloalkyl-C₀₋₆alkyl;

R'' is R', -C(O)R' or -C(O)OR';

10 R''' is H, C₁₋₆alkyl, Ar-C₀₋₆alkyl, Het-C₀₋₆alkyl, or C₃₋₆cycloalkyl-C₀₋₆alkyl, halogen, CF₃, OR^f, S(O)_kR^f, COR^f, NO₂, N(R^f)₂, CO(NR^f)₂, CH₂N(R^f)₂;

R^y is H, halo, -OR^g, -SR^g, -CN, -NR^gR^k, -NO₂, -CF₃, CF₃S(O)_r, -CO₂R^g, -COR^g or -CONR^g₂, or C₁₋₆alkyl optionally substituted by halo, -OR^g, -SR^g, -CN, -NR^gR'', -NO₂, -CF₃, R'S(O)_r, -CO₂R^g, -COR^g or -CONR^g₂;

a is 0, 1 or 2;

15 b is 0, 1 or 2;

k is 0, 1 or 2;

m is 1 or 2;

r is 0, 1 or 2;

s is 0, 1 or 2;

20 u is 0 or 1; and

v is 0 or 1;

or a pharmaceutically acceptable salt thereof.

Representative of the novel prodrugs of this invention are the following:

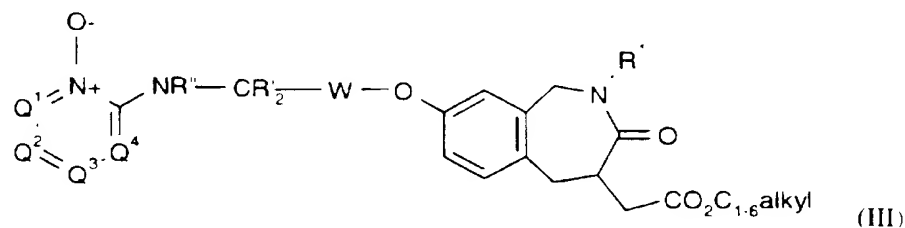
25 methyl (±)-3-oxo-8-[3-(pyridin-2-ylamino)-1-propyloxy]-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetate; and

ethyl (±)-8-[3-(4-aminopyridin-2-ylamino)-1-propyloxy]-3-oxo-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetate;

or a pharmaceutically acceptable salt thereof.

In yet another aspect of this invention are novel intermediates of formula (III):

30



- R^1 is R^7 , or A-C₀₋₄alkyl, A-C₂₋₄alkenyl, A-C₂₋₄alkynyl, A-C₃₋₄oxoalkenyl, A-C₃₋₄oxoalkynyl, A-C₁₋₄aminoalkyl, A-C₃₋₄aminoalkenyl, A-C₃₋₄aminoalkynyl, optionally substituted by any accessible combination of one or more of R^{10} or R^7 ;
- A is H, C₃₋₆cycloalkyl, Het or Ar;
- 5 R^7 is -COR⁸, -COCR'₂R⁹, -C(S)R⁸, -S(O)_mOR', -S(O)_mNR'R'', -PO(OR'), -PO(OR')₂, -NO₂, or tetrazolyl;
- each R⁸ independently is -OR', -NR'R'', -NR'SO₂R', -NR'OR', or -OCR'₂CO(O)R';
- R⁹ is -OR', -CN, -S(O)_rR', -S(O)_mNR'₂, -C(O)R', C(O)NR'₂, or -CO₂R';
- R¹⁰ is H, halo, -OR¹¹, -CN, -NR'R¹¹, -NO₂, -CF₃, CF₃S(O)_r-, -CO₂R', -CONR'₂,
- 10 A-C₀₋₆alkyl-, A-C₁₋₆oxoalkyl-, A-C₂₋₆alkenyl-, A-C₂₋₆alkynyl-, A-C₀₋₆alkyloxy-, A-C₀₋₆alkylamino- or A-C₀₋₆alkyl-S(O)_r-;
- R¹¹ is R', -C(O)R', -C(O)NR'₂, -C(O)OR', -S(O)_mR', or -S(O)_mNR'₂;
- W is -(CHR^g)_a-U-(CHR^g)_b-;
- U is absent or CO, CR^g₂, C(=CR^g₂), S(O)_k, O, NR^g, CR^gOR^g, CR^g(OR^k)CR^g₂,
- 15 CR^g₂CR^g(OR^k), C(O)CR^g₂, CR^g₂C(O), CONRⁱ, NRⁱCO, OC(O), C(O)O, C(S)O, OC(S), C(S)NR^g, NR^gC(S), S(O)₂NR^g, NR^gS(O)₂N=N, NR^gNR^g, NR^gCR^g₂, CR^g₂NR^g, CR^g₂O, OCR^g₂, C≡C or CR^g=CR^g;
- R^g is H, C₁₋₆alkyl, Het-C₀₋₆alkyl, C₃₋₇cycloalkyl-C₀₋₆alkyl or Ar-C₀₋₆alkyl;
- R^k is R^g, -C(O)R^g, or -C(O)OR^f;
- 20 Rⁱ is H, C₁₋₆alkyl, Het-C₀₋₆alkyl, C₃₋₇cycloalkyl-C₀₋₆alkyl, Ar-C₀₋₆alkyl, or C₁₋₆alkyl substituted by one to three groups chosen from halogen, CN, NR^g₂, OR^g, SR^g, CO₂R^g, and CON(R^g)₂;
- R^f is H, C₁₋₆alkyl or Ar-C₀₋₆alkyl;
- Q¹, Q², Q³ and Q⁴ are independently N or C-R^y, provided that no more than one of
- 25 Q¹, Q², Q³ and Q⁴ is N;
- R' is H, C₁₋₆alkyl, Ar-C₀₋₆alkyl or C₃₋₆cycloalkyl-C₀₋₆alkyl;
- R'' is R', -C(O)R' or -C(O)OR';
- R^y is H, halo, -OR^g, -SR^g, -CN, -NR^gR^k, -NO₂, -CF₃, CF₃S(O)_r-, -CO₂R^g, -COR^g or -CONR^g₂, or C₁₋₆alkyl optionally substituted by halo, -OR^g, -SR^g, -CN, -NR^gR'', -NO₂,
- 30 -CF₃, R'S(O)_r-, -CO₂R^g, -COR^g or -CONR^g₂;
- a is 0, 1 or 2;
- b is 0, 1 or 2;
- m is 1 or 2; and
- r is 0, 1 or 2;
- 35 or a pharmaceutically acceptable salt thereof.

Abbreviations and symbols commonly used in the peptide and chemical arts are used herein to describe the compounds of this invention. In general, the amino acid

abbreviations follow the IUPAC-IUB Joint Commission on Biochemical Nomenclature as described in *Eur. J. Biochem.*, 158, 9 (1984).

C₁₋₄alkyl as applied herein means an optionally substituted alkyl group of 1 to 4 carbon atoms, and includes methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl and t-butyl.

- 5 C₁₋₆alkyl additionally includes pentyl, n-pentyl, isopentyl, neopentyl and hexyl and the simple aliphatic isomers thereof. C₀₋₄alkyl and C₀₋₆alkyl additionally indicates that no alkyl group need be present (e.g., that a covalent bond is present).

- Any C₁₋₄alkyl or C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl or C₁₋₆ oxoalkyl may be optionally substituted with the group R^x, which may be on any carbon atom that results in a stable structure and is available by conventional synthetic techniques. Suitable groups for R^x are C₁₋₄alkyl, OR', SR', C₁₋₄alkylsulfonyl, C₁₋₄alkylsulfoxyl, -CN, N(R')₂, CH₂N(R')₂, -NO₂, -CF₃, -CO₂R', -CON(R')₂, -COR', -NR'C(O)R', F, Cl, Br, I, or CF₃S(O)_r-, wherein r is 0, 1 or 2.

Halogen or halo means F, Cl, Br, and I.

- 15 Ar, or aryl, as applied herein, means phenyl or naphthyl, or phenyl or naphthyl substituted by one to three substituents, such as those defined above for alkyl, especially C₁₋₄alkyl, C₁₋₄alkoxy, C₁₋₄alkthio, CF₃, NH₂, OH, F, Cl, Br or I.

- Het, or heterocycle, indicates an optionally substituted five or six membered monocyclic ring, or a nine or ten-membered bicyclic ring containing one to three heteroatoms chosen from the group of nitrogen, oxygen and sulfur, which are stable and available by conventional chemical synthesis. Illustrative heterocycles are benzofuryl, benzimidazole, benzopyran, benzothiophene, furan, imidazole, indoline, morpholine, piperidine, piperazine, pyrrole, pyrrolidine, tetrahydropyridine, pyridine, thiazole, thiophene, quinoline, isoquinoline, and tetra- and perhydro- quinoline and isoquinoline.
- 25 Any accessible combination of up to three substituents on the Het ring, such as those defined above for alkyl that are available by chemical synthesis and are stable are within the scope of this invention.

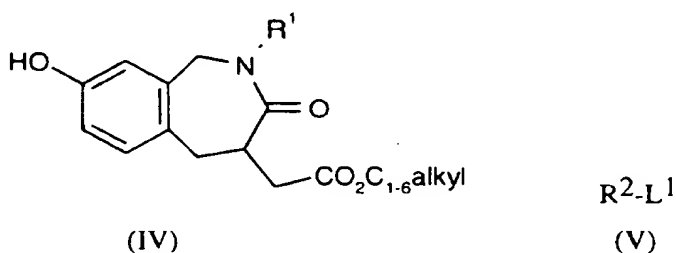
- C₃₋₇cycloalkyl refers to an optionally substituted carbocyclic system of three to seven carbon atoms, which may contain up to two unsaturated carbon-carbon bonds.
- 30 Typical of C₃₋₇cycloalkyl are cyclopropyl, cyclobutyl, cyclopentyl, cyclopentenyl, cyclohexyl, cyclohexenyl and cycloheptyl. Any combination of up to three substituents, such as those defined above for alkyl, on the cycloalkyl ring that is available by conventional chemical synthesis and is stable, is within the scope of this invention

- When R^b and R^c are joined together to form a five- or six-membered aromatic or non-aromatic carbocyclic or heterocyclic ring fused to the ring to which R^b and R^c are attached, the ring formed will generally be a five- or six-membered heterocycle selected from those listed above for Het, or will be a phenyl, cyclohexyl or cyclopentyl ring
- 35

Preferably R_b and R_c will be $-D1=D2-D3=D4$ wherein $D1 - D4$ are independently CH, N or $C-R_x$ with the proviso that no more than two of $D1 - D4$ are N. Most preferably, when R^b and R^c are joined together they form the group $-CH=CH-CH=CH-$.

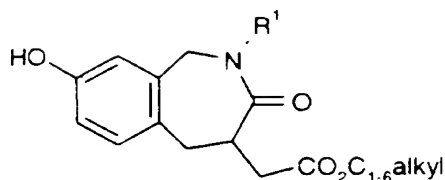
- Certain radical groups are abbreviated herein. t-Bu refers to the tertiary butyl radical, Boc refers to the t-butyloxycarbonyl radical, Fmoc refers to the fluorenylmethoxycarbonyl radical, Ph refers to the phenyl radical, Cbz refers to the benzyloxycarbonyl radical, Bn refers to the benzyl radical, Me refers to methyl, Et refers to ethyl, Ac refers to acetyl, Alk refers to C_{1-4} alkyl, Nph refers to 1- or 2-naphthyl and cHex refers to cyclohexyl. Tet refers to 5-tetrazolyl.
- Certain reagents are abbreviated herein. DCC refers to dicyclohexylcarbodiimide, DMAP refers to dimethylaminopyridine, DIEA refers to diisopropylethyl amine, EDC refers to 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide, hydrochloride. HOBt refers to 1-hydroxybenzotriazole, THF refers to tetrahydrofuran, DIEA refers to diisopropylethylamine, DEAD refers to diethyl azodicarboxylate, PPh_3 refers to triphenylphosphine, DIAD refers to diisopropyl azodicarboxylate, DME refers to dimethoxyethane, DMF refers to dimethylformamide, NBS refers to N-bromosuccinimide, Pd/C refers to a palladium on carbon catalyst, PPA refers to polyphosphoric acid, DPPA refers to diphenylphosphoryl azide, BOP refers to benzotriazol-1-yloxy-tris(dimethyl-amino)phosphonium hexafluorophosphate, HF refers to hydrofluoric acid, TEA refers to triethylamine, TFA refers to trifluoroacetic acid, PCC refers to pyridinium chlorochromate.

The compounds of formula (I) are generally prepared by reacting a compound of formula (IV) with a compound of formula (V):

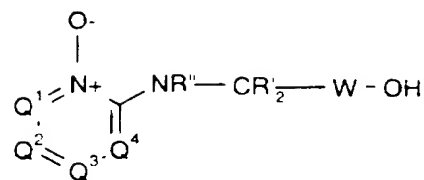


- wherein R^1 and R^2 are as defined in formula (I), with any reactive functional groups protected, and L^1 is OH or halo; and thereafter removing any protecting groups, and optionally forming a pharmaceutically acceptable salt.

- Suitably, certain compounds of formula (I) are prepared by reacting a compound of formula (IV) with a compound of formula (VI):



(IV)



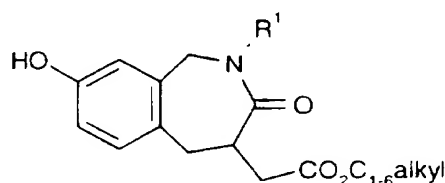
(VI)

wherein R^1 , R' , R'' , W , Q^1 , Q^2 , Q^3 and Q^4 are as defined in formula (I), with any
 5 reactive functional groups protected;

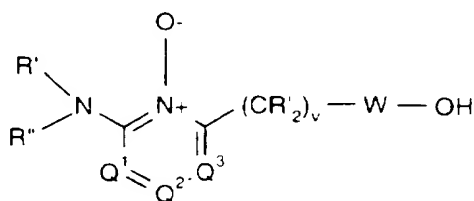
and thereafter removing any protecting groups, and optionally forming a
 pharmaceutically acceptable salt.

Preferably, for formula (VI) compounds, Q^1 , Q^2 , Q^3 and Q^4 are CH, W is $-\text{CH}_2-$
 CH_2- , R' is H and R'' is H, $\text{C}_{1-4}\text{alkyl}$ or $-\text{C}(\text{O})\text{OC}_{1-4}\text{alkyl}$. Suitably, the reaction between a
 10 compound of formula (IV) with a compound of formula (VI) is carried out in the presence
 of diethyl azodicarboxylate and triphenylphosphine in an aprotic solvent.

Additionally, certain compounds of formula (I) are prepared by reacting a
 compound of formula (IV) with a compound of formula (VII):



(IV)



(VII)

15

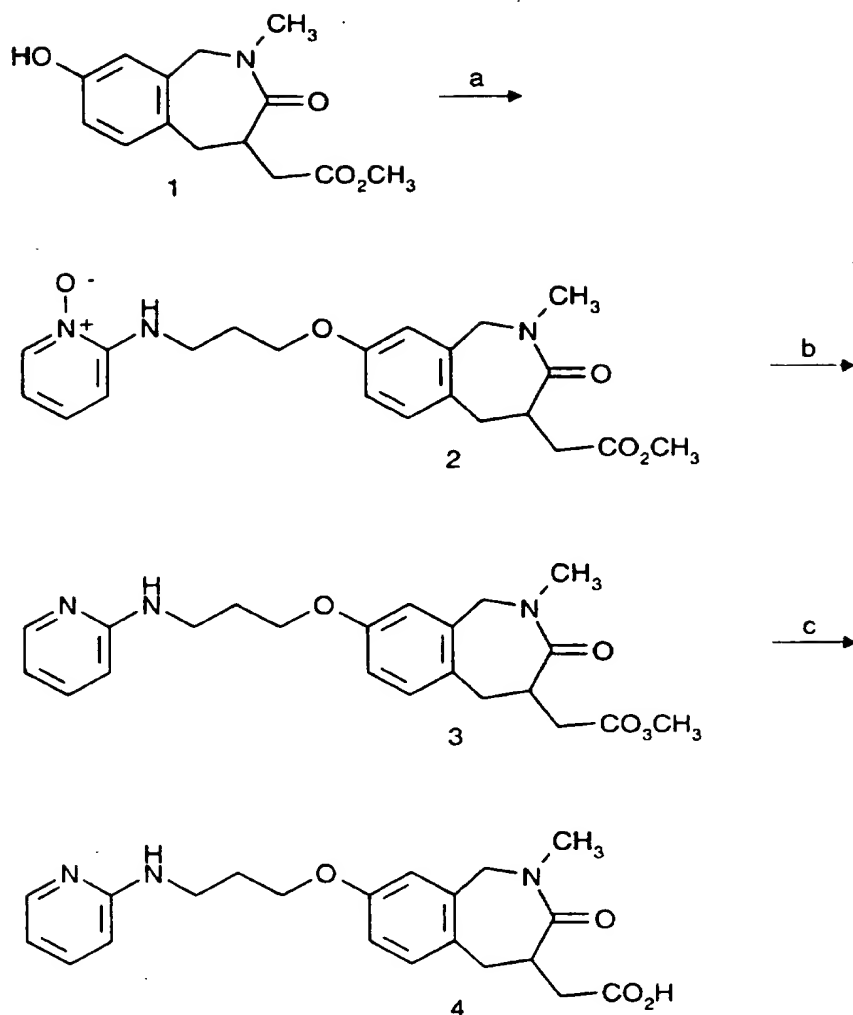
wherein R^1 , R' , R'' , W , Q^1 , Q^2 , Q^3 and v are as defined in formula (I), with any
 reactive functional groups protected;

20 and thereafter removing any protecting groups, and optionally forming a
 pharmaceutically acceptable salt.

Preferably, for formula (VII) compounds, Q^1 , Q^2 and Q^3 are CH, W is $-\text{CH}_2-\text{CH}_2-$,
 v is 0, R' is H and R'' is H or $\text{C}_{1-4}\text{alkyl}$. Suitably, the reaction between a compound of
 formula (IV) with a compound of formula (VII) is carried out in the presence of diethyl
 25 azodicarboxylate and triphenylphosphine in an aprotic solvent.

Compounds of the formula (I) are prepared by the general methods described in
 Schemes I-VII.

Scheme I



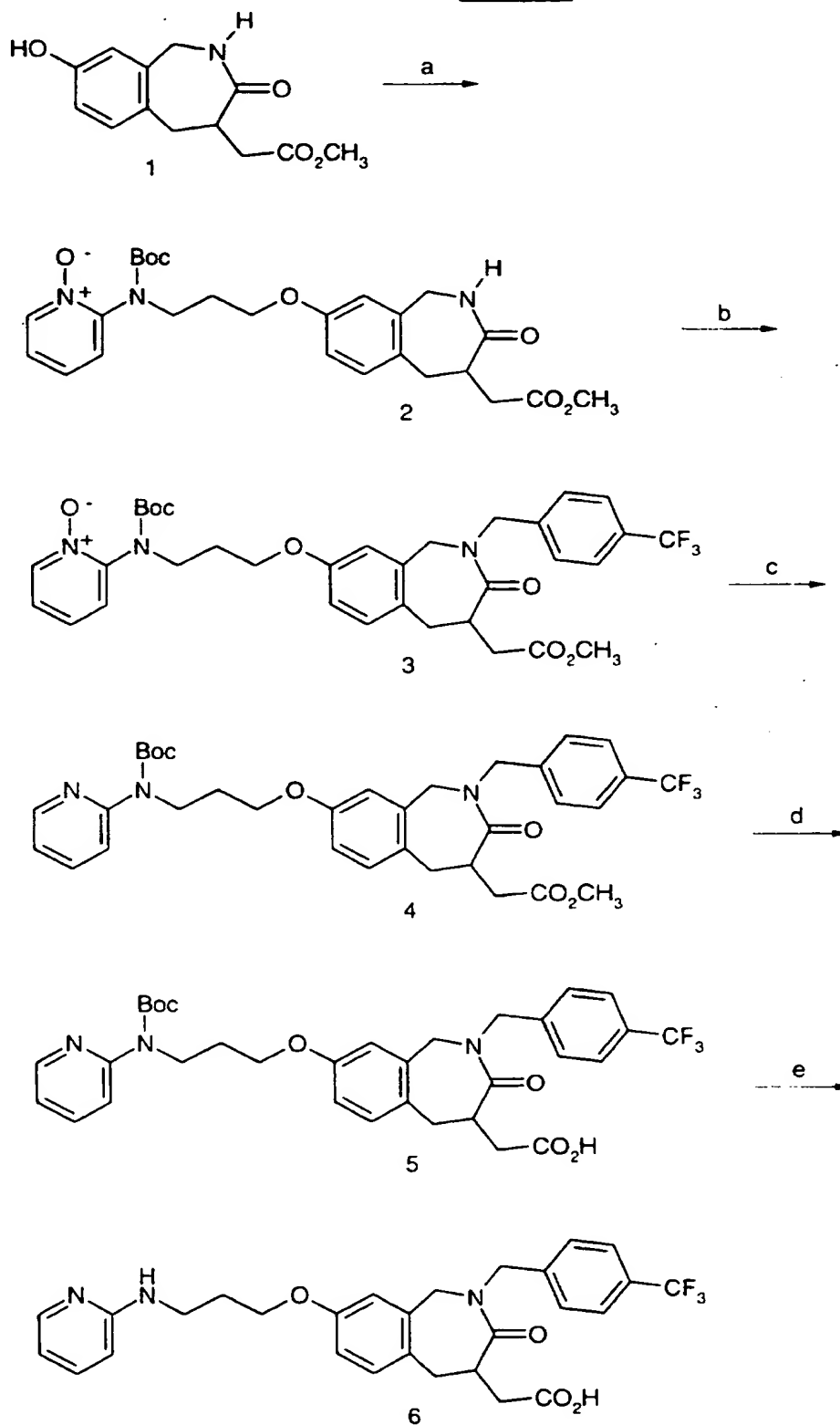
- 5 a) 2-[(3-hydroxy-1-propyl)amino]pyridine-N-oxide, DEAD, (Ph)₃P, DMF; b) cyclohexene, 10% Pd/C, 2-propanol; c) 1.0 N LiOH, THF, H₂O, then acidification.

Compound **I-1**, the preparation of which follows the general procedures outlined in Bondinell, et al. (WO 93/00095), is reacted with 2-[(3-hydroxy-1-propyl)amino]pyridine-N-oxide in a Mitsunobu-type coupling reaction (*Organic Reactions* **1992**, 42, 335-656; *Synthesis* **1981**, 1-28) to afford **I-2**. The reaction is mediated by the complex formed between diethyl azodicarboxylate and triphenylphosphine, and is conducted in an aprotic solvent, for instance THF, CH₂Cl₂, or DMF. The pyridine-N-oxide moiety of **I-2** is reduced to the corresponding pyridine **I-3** under transfer hydrogenation conditions using a palladium catalyst, preferably palladium metal on activated carbon, in an inert solvent, for instance methanol, ethanol, or 2-propanol. Cyclohexene, 1,4-cyclohexadiene, formic acid,

and salts of formic acid, such as potassium formate or ammonium formate, are commonly used as the hydrogen transfer reagent in this type of reaction. The methyl ester of **I-3** is hydrolyzed using aqueous base, for example, LiOH in aqueous THF or NaOH in aqueous methanol or ethanol, and the intermediate carboxylate salt is acidified with a suitable acid, for instance TFA or HCl, to afford the carboxylic acid **I-4**. Alternatively, the intermediate carboxylate salt can be isolated, if desired, or a carboxylate salt of the free carboxylic acid can be prepared by methods well-known to those of skill in the art.

Compounds of formula (I) may also be prepared by alternate methods known to those skilled in the art. For example, the ether linkage of formula (I) compounds may be formed by reacting the alcohol group of a formula 1-Scheme 1 compound with a R²-compound containing a displaceable group, such as a chloro, bromo or iodo group. Other ether-forming reactions can be employed and should be readily apparent to those skilled in the art.

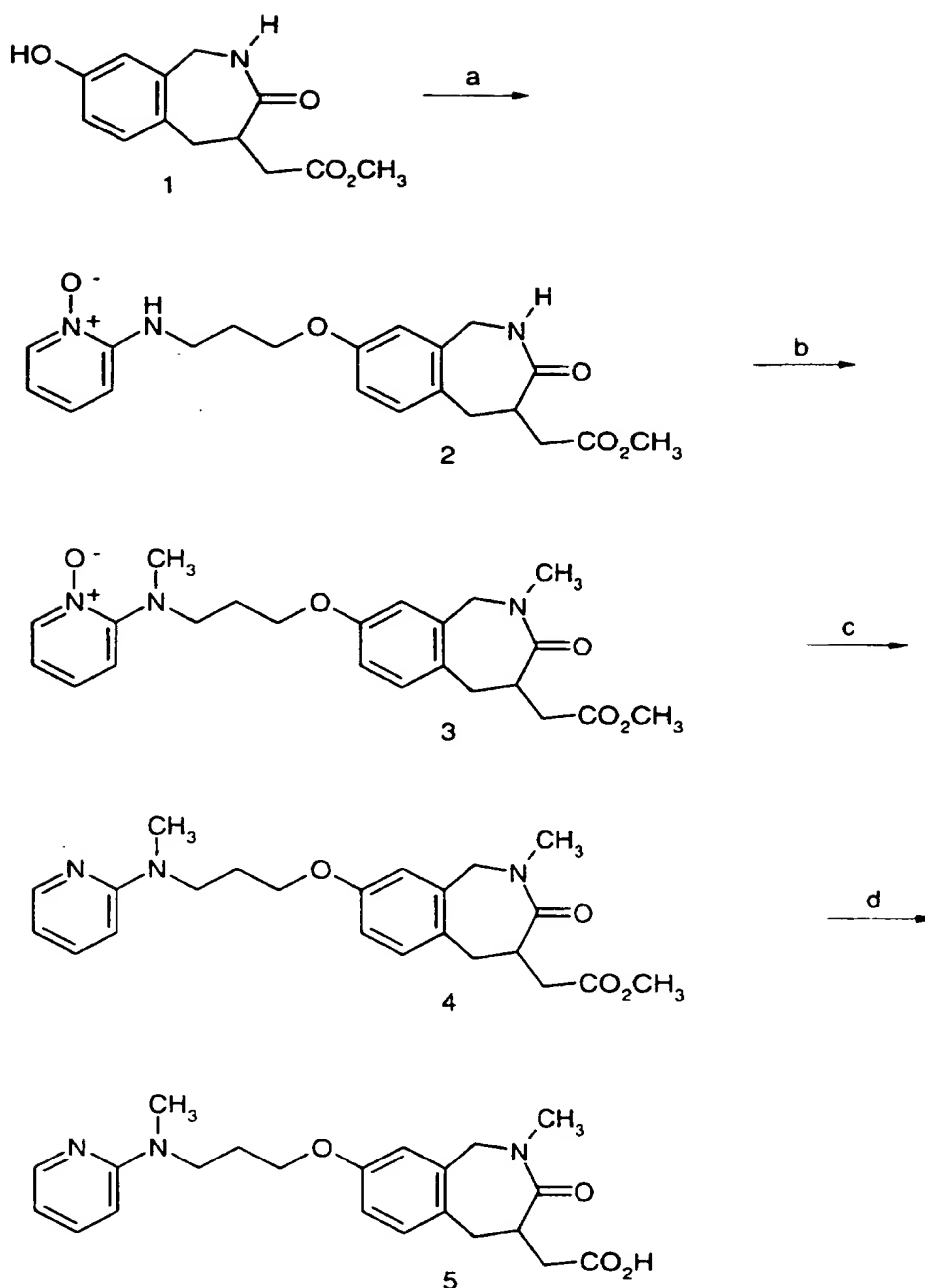
Scheme II



a) 2-[N-(3-hydroxy-1-propyl)-N-(*tert*-butoxycarbonyl)amino]pyridine-N-oxide, DEAD, (Ph)₃P, DMF; b) LiHMDS, 4-trifluoromethylbenzyl bromide, DMF; c) cyclohexene, 10% Pd/C, 2-propanol; d) 1.0 N NaOH, MeOH; e) HCl/dioxane;

5 Compound **II-1**, prepared as described in Scheme I, is reacted with 2-[N-(3-hydroxy-1-propyl)-N-(*tert*-butoxycarbonyl)amino pyridine-N-oxide in a Mitsunobu-type coupling reaction as described in detail in Scheme I. The resulting product, **II-2**, can be alkylated at position 2 (benzazepine numbering) under standard alkylation conditions well-known to those of skill in the art. For example, **II-2** can be treated with a base, such as
10 sodium hydride, LDA, or lithium hexamethyldisilazide, in an appropriate solvent, usually THF, DMF, DME, or mixtures thereof, to effect deprotonation of the amide N-H. Treatment of the resulting anionic species with an appropriate electrophile, such as an alkyl or benzyl halide, results in N-alkylation to afford the product, for example **II-3**. The N-oxide of **II-3** can be reduced as described in Scheme I to afford **II-4**, which can be
15 saponified to **II-5** as described in Scheme I. Deprotection of **II-5** to afford **II-6** is accomplished under standard acidic conditions as described in Greene, "Protective Groups in Organic Synthesis" (published by Wiley-Interscience). Such conditions are well-known to those of skill in the art. Alternatively, conversion of **II-3** to **II-6** can be accomplished by an alternate sequence, for example initial Boc deprotection of **II-3**, followed by reduction
20 of the N-oxide, and finally saponification.

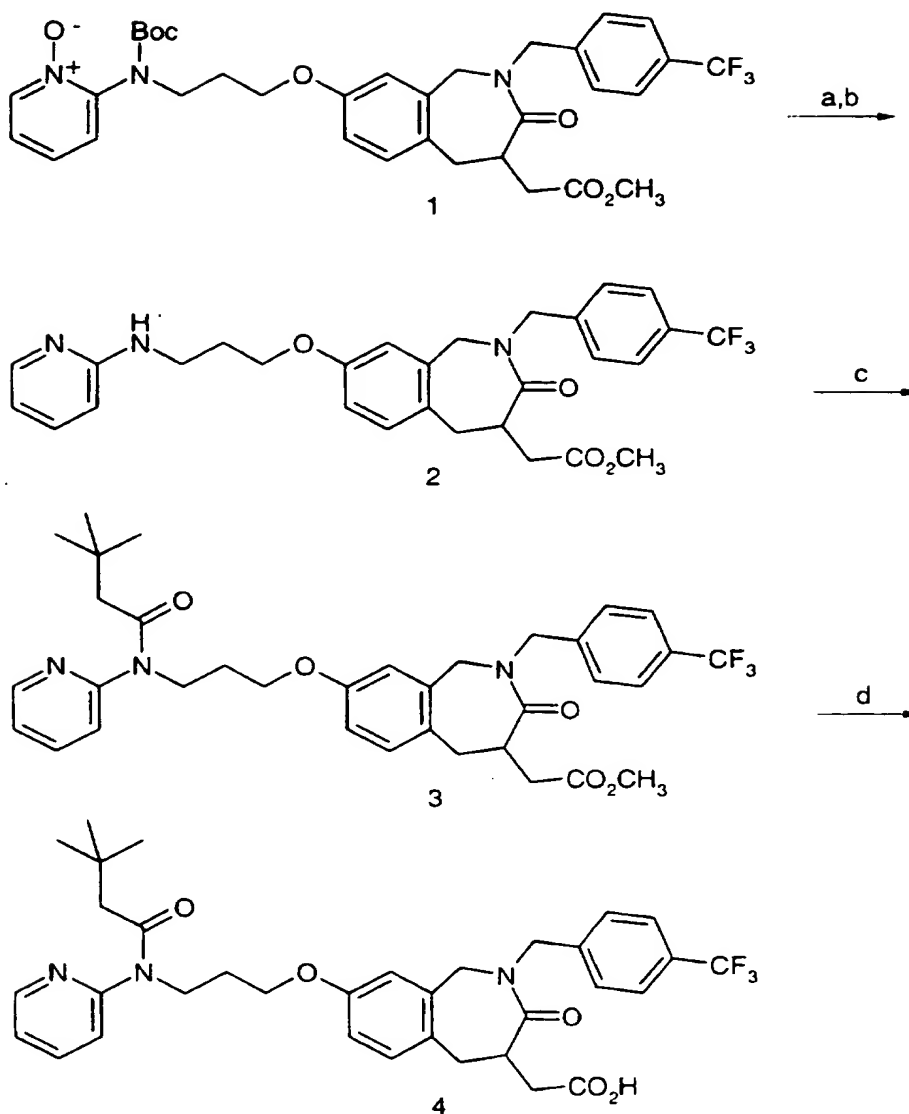
Scheme III



- 5 a) 2-[(3-hydroxy-1-propyl)amino]pyridine-N-oxide, DEAD, (Ph)₃P, DMF; b) LiHMDS, CH₃I, DMF; c) cyclohexene, 10% Pd/C, 2-propanol; d) 1.0 N NaOH, MeOH, then acidification.

Compound **III-2**, prepared as described in Scheme I, can be alkylated simultaneously at both position 2 (benzazepine numbering) and on the nitrogen attached to the pyridine ring under standard alkylation conditions well-known to those of skill in the art. For example, **III-2** can be treated with at least 2 molar equivalents of a base, such as sodium hydride, LDA, or lithium hexamethyldisilazide, in an appropriate solvent, usually THF, DMF, DME, or mixtures thereof, to effect deprotonation. Treatment of the resulting anionic species with an excess of an appropriate electrophile, such as an alkyl or benzyl halide, results in bis-alkylation to afford the product, for example **III-3**. Conversion of **III-3** to **III-5** follows the methods described in Schemes I and II.

Scheme IV



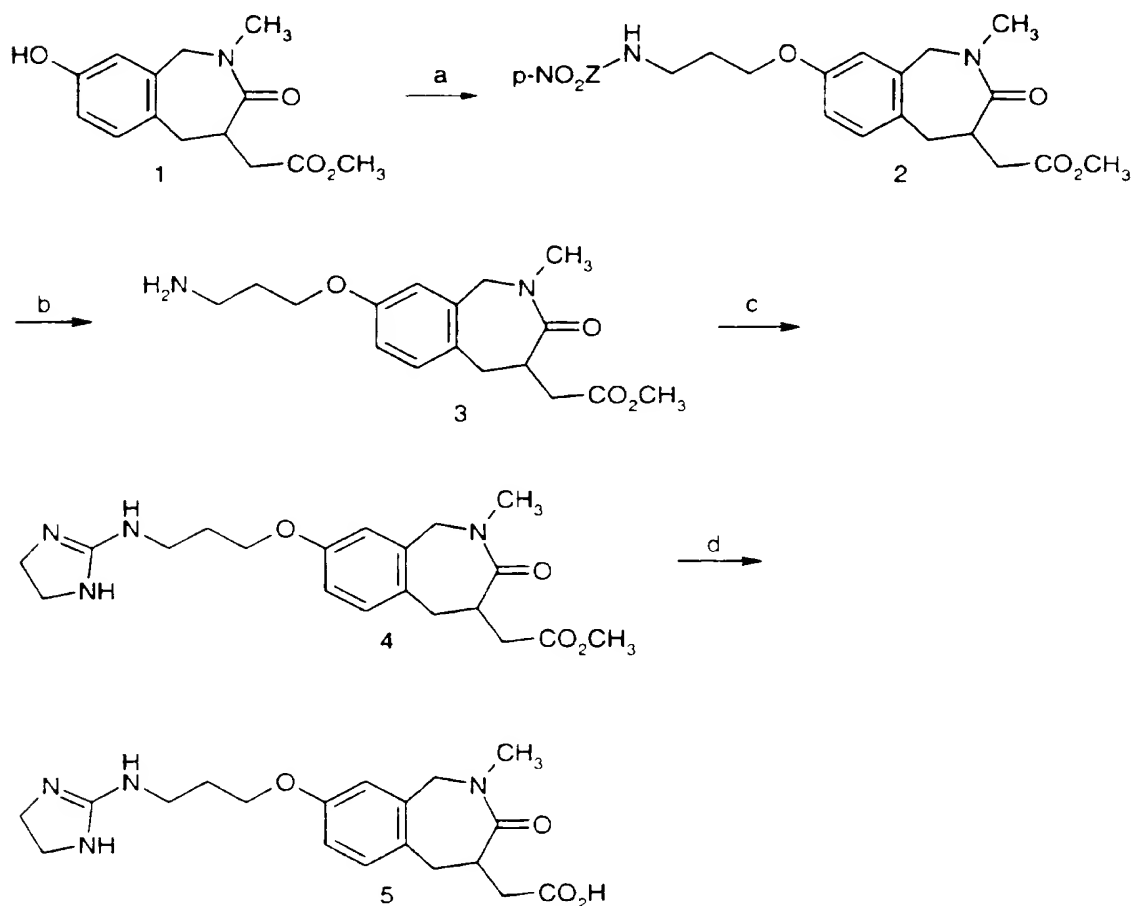
- 5 a) cyclohexene, 10% Pd/C, 2-propanol; b) HCl/dioxane; c) *tert*-butylacetyl chloride, Et₃N, CH₂Cl₂; d) 1.0 N NaOH, MeOH, then acidification.

Compound IV-2, prepared from IV-1 by the procedures outlined in Schemes I - III, can be acylated at the nitrogen atom attached to the pyridine ring under standard acylation conditions well-known to those of skill in the art. For example, reaction of IV-2 with an acylating agent, for instance *tert*-butylacetyl chloride, in the presence of an appropriate acid scavenger, generally triethylamine, diisopropylethylamine, or pyridine, in a suitable solvent, oftentimes CH₂Cl₂, provides IV-3. Many additional methods for acylation of an

amine are known, and can be found in standard reference books, such as "Compendium of Organic Synthetic Methods", Vol. I - VI (published by Wiley-Interscience). Saponification of IV-3 as described in Schemes I - III affords IV-4.

5

Scheme V

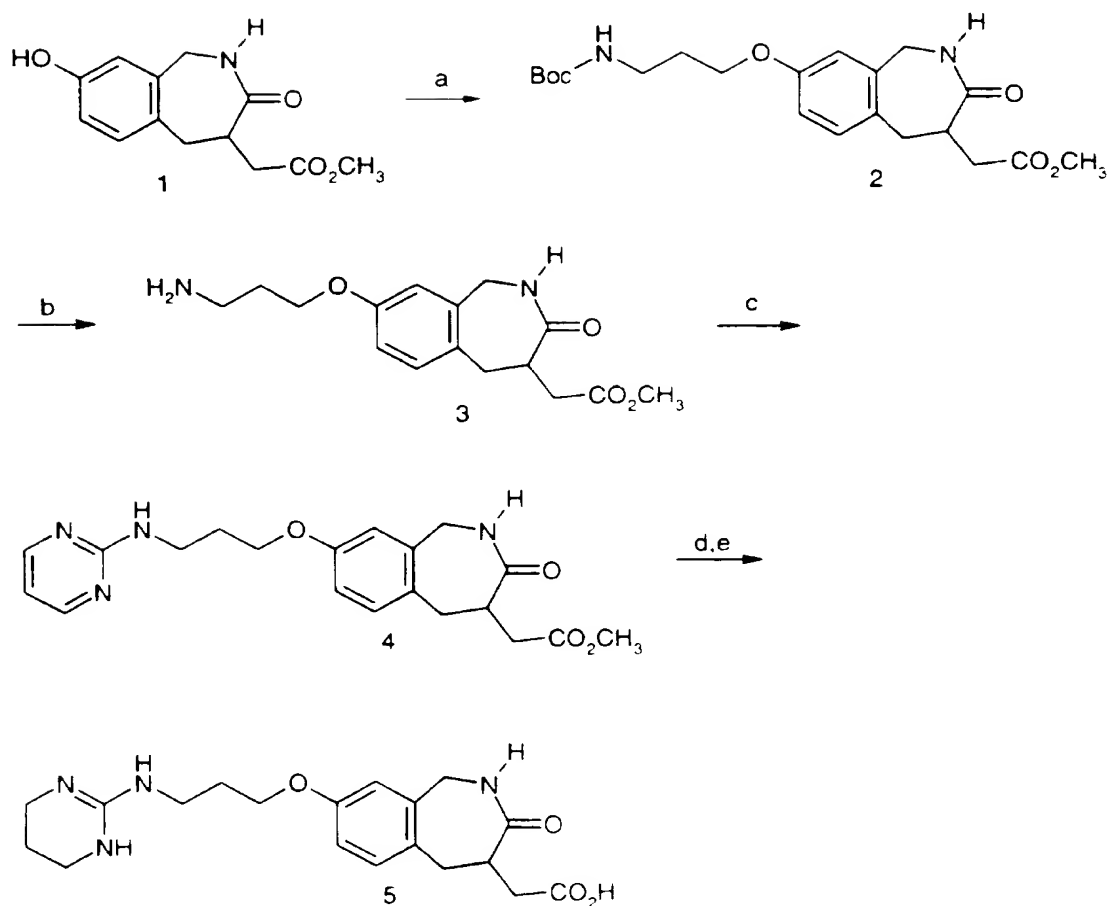


- 10 a) 3-(4-nitrobenzyloxycarbonylamino)-1-propanol, DEAD, $(\text{Ph})_3\text{P}$, DMF, CH_2Cl_2 ; b) H_2 , Pd/C , EtOH; c) 2-methylthio-2-imidazoline hydriodide, $(i\text{-Pr})_2\text{NEt}$, dimethylacetamide, 100°C ; d) 1.0 N LiOH, THF, H_2O , then acidification.

- 15 Compound V-1, prepared as described in Scheme I, is reacted with a protected version of 3-amino-1-propanol, such as 3-(*tert*-butoxycarbonylamino)-1-propanol, 3-(benzyloxycarbonylamino)-1-propanol, or 3-(4-nitrobenzyloxycarbonylamino)-1-propanol, in a Mitsunobu-type coupling reaction as described in Scheme I. The resulting compound,

V-2, is deprotected to afford V-3. As is well-known to those of skill in the art, deprotection conditions are selected based on the functionality and protecting group present in V-2. For example, the *p*-nitro-Cbz group present in V-2 is removed by hydrogenolysis in the presence of a palladium catalyst, generally palladium on charcoal or Pd(OH)₂ on charcoal, in an appropriate solvent, usually methanol, ethanol, ethyl acetate, or mixtures thereof. If desired, the hydrogenolysis can be conducted in the presence of an acid, for example HCl, to obtain the corresponding ammonium salt of V-2. Reaction of V-3 with 2-methylthio-2-imidazoline hydriodide in the presence of a base, for instance diisopropylethylamine, in a suitable solvent, such as MeOH, EtOH, DMF or dimethylacetamide, provides V-4. Similar conditions for effecting a related transformation are described in WO 95/32710. Saponification to afford V-5 is accomplished as described in Scheme I.

Scheme VI



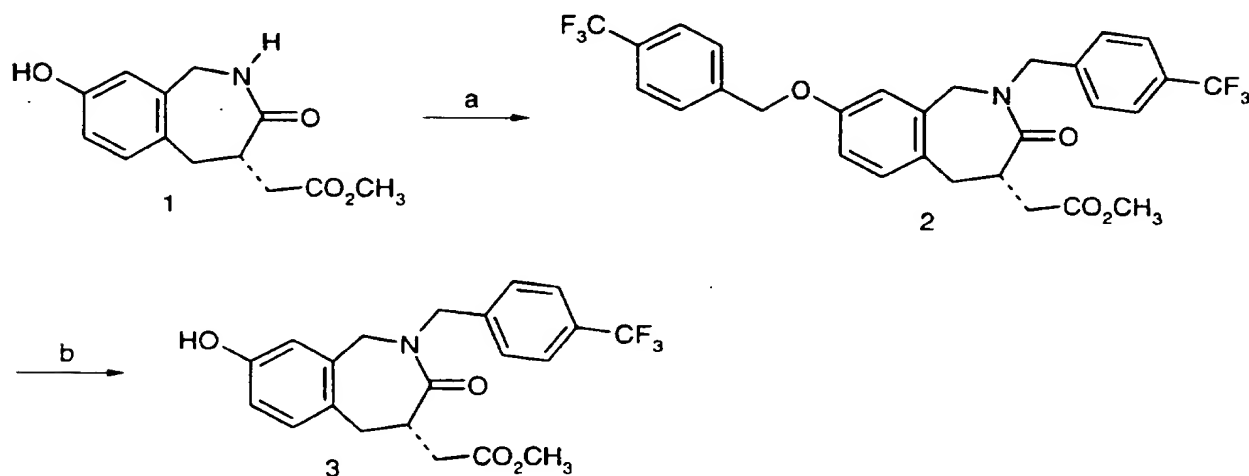
- 5 a) 3-(*tert*-butoxycarbonylamino)-1-propanol, DEAD, (Ph)₃P, DMF, THF; b) TFA, CH₂Cl₂; c) 2-bromopyrimidine, NaHCO₃, EtOH, reflux; d) H₂, Pd/C, HCl, MeOH; e) K₂CO₃, H₂O.

Compound VI-3, prepared from VI-1 by the procedure outlined in Scheme V, is reacted with a 2-halopyrimidine, generally 2-chloropyrimidine or 2-bromopyrimidine, in the presence of a suitable acid scavenger, usually sodium bicarbonate, triethylamine, diisopropylethylamine, or pyridine, in a suitable solvent, such as ethanol, DMF, or dimethylacetamide, to provide VI-4. The pyrimidine ring of VI-4 is reduced to the corresponding 1,4,5,6-tetrahydropyrimidine ring according to conditions reported for effecting such a transformation (see, for example, WO 95/32710). Thus, VI-4 is subjected to hydrogenation in the presence of a palladium catalyst, preferably palladium on activated carbon, in an appropriate solvent, such as methanol or ethanol. The reaction is usually

conducted under acidic conditions; addition of a mineral acid such as HCl is generally preferable. VI-5 is obtained following basification of the filtered reaction mixture with K_2CO_3 and H_2O .

5

Scheme VII



a) NaH, 4-(trifluoromethyl)benzyl bromide, DMF; b) H_2 , $Pd(OH)_2/C$, MeOH.

10

Compound VII-1, prepared by the general procedures described in Bondinell, et al., PCT application WO 93/00095, published January 7, 1993 and Bondinell, et al., PCT application WO 94/14776, is reacted with 4-(trifluoromethyl)benzyl bromide in the presence of a suitable base, generally sodium hydride or lithium bis(trimethylsilyl)amide, in an aprotic solvent, preferably DMF, THF, or mixtures thereof, to afford the bis-alkylated product VII-2. The 4-(trifluoromethyl)benzyl ether of VII-2 can be conveniently removed by hydrogenolysis to provide the phenol VII-3. Methods for hydrogenolysis of benzyl ethers are well-known to those of skill in the art, and are described in appropriate reference volumes, for instance in Greene, "Protective Groups in Organic Synthesis" (published by Wiley-Interscience). The phenol of VII-3 is then used to prepare the formula (I) compounds using the methods described in the previous schemes.

15

20

Amide coupling reagents as used herein denote reagents which may be used to form peptide bonds. Typical coupling methods employ carbodiimides, activated anhydrides and esters and acyl halides. Reagents such as EDC, DCC, DPPA, PPA, BOP reagent, HOBt, N-hydroxysuccinimide and oxalyl chloride are typical.

25

Coupling methods to form peptide bonds are generally well known to the art. The methods of peptide synthesis generally set forth by Bodansky *et al.*, THE PRACTICE OF

PEPTIDE SYNTHESIS, Springer-Verlag, Berlin, 1984, Ali *et al.* in *J. Med. Chem.*, 29, 984 (1986) and *J. Med. Chem.*, 30, 2291 (1987) are generally illustrative of the technique and are incorporated herein by reference.

Typically, the amine or aniline is coupled via its free amino group to an appropriate
5 carboxylic acid substrate using a suitable carbodiimide coupling agent, such as N,N'-
dicyclohexyl carbodiimide (DCC), optionally in the presence of catalysts such as 1-
hydroxybenzotriazole (HOBt) and dimethylamino pyridine (DMAP). Other methods, such
as the formation of activated esters, anhydrides or acid halides, of the free carboxyl of a
suitably protected acid substrate, and subsequent reaction with the free amine of a suitably
10 protected amine, optionally in the presence of a base, are also suitable. For example, a
protected Boc-amino acid or Cbz-amidino benzoic acid is treated in an anhydrous solvent,
such as methylene chloride or tetrahydrofuran(THF), in the presence of a base, such as N-
methyl morpholine, DMAP or a trialkylamine, with isobutyl chloroformate to form the
"activated anhydride", which is subsequently reacted with the free amine of a second
15 protected amino acid or aniline.

Useful intermediates for preparing formula (I) compounds in which R² is a
benzimidazole are disclosed in Nestor *et al.*, *J. Med. Chem.* **1984**, 27, 320. Representative
methods for preparing benzimidazole compounds useful as intermediates in the present
invention are also common to the art and may be found, for instance, in EP-A 0 381 033.

20 Acid addition salts of the compounds are prepared in a standard manner in a
suitable solvent from the parent compound and an excess of an acid, such as hydrochloric,
hydrobromic, hydrofluoric, sulfuric, phosphoric, acetic, trifluoroacetic, maleic, succinic or
methanesulfonic. Certain of the compounds form inner salts or zwitterions which may be
acceptable. Cationic salts are prepared by treating the parent compound with an excess of
25 an alkaline reagent, such as a hydroxide, carbonate or alkoxide, containing the appropriate
cation; or with an appropriate organic amine. Cations such as Li⁺, Na⁺, K⁺, Ca⁺⁺, Mg⁺⁺
and NH₄⁺ are specific examples of cations present in pharmaceutically acceptable salts.

This invention also provides a pharmaceutical composition which comprises a
compound according to formula (I) and a pharmaceutically acceptable carrier.

30 Accordingly, the compounds of formula (I) may be used in the manufacture of a
medicament. Pharmaceutical compositions of the compounds of formula (I) prepared as
hereinbefore described may be formulated as solutions or lyophilized powders for
parenteral administration. Powders may be reconstituted by addition of a suitable diluent
or other pharmaceutically acceptable carrier prior to use. The liquid formulation may be a
35 buffered, isotonic, aqueous solution. Examples of suitable diluents are normal isotonic
saline solution, standard 5% dextrose in water or buffered sodium or ammonium acetate
solution. Such formulation is especially suitable for parenteral administration, but may also

be used for oral administration or contained in a metered dose inhaler or nebulizer for insufflation. It may be desirable to add excipients such as polyvinylpyrrolidone, gelatin, hydroxy cellulose, acacia, polyethylene glycol, mannitol, sodium chloride or sodium citrate.

5 Alternately, these compounds may be encapsulated, tableted or prepared in a emulsion or syrup for oral administration. Pharmaceutically acceptable solid or liquid carriers may be added to enhance or stabilize the composition, or to facilitate preparation of the composition. Solid carriers include starch, lactose, calcium sulfate dihydrate, terra alba, magnesium stearate or stearic acid, talc, pectin, acacia, agar or gelatin. Liquid carriers
10 include syrup, peanut oil, olive oil, saline and water. The carrier may also include a sustained release material such as glyceryl monostearate or glyceryl distearate, alone or with a wax. The amount of solid carrier varies but, preferably, will be between about 20 mg to about 1 g per dosage unit. The pharmaceutical preparations are made following the conventional techniques of pharmacy involving milling, mixing, granulating, and
15 compressing, when necessary, for tablet forms; or milling, mixing and filling for hard gelatin capsule forms. When a liquid carrier is used, the preparation will be in the form of a syrup, elixir, emulsion or an aqueous or non-aqueous suspension. Such a liquid formulation may be administered directly p.o. or filled into a soft gelatin capsule.

For rectal administration, the compounds of this invention may also be combined
20 with excipients such as cocoa butter, glycerin, gelatin or polyethylene glycols and molded into a suppository.

The compounds described herein are antagonists of the vitronectin receptor, and are useful for treating diseases wherein the underlying pathology is attributable to ligand or cell which interacts with the vitronectin receptor. For instance, these compounds are useful for
25 the treatment of diseases wherein loss of the bone matrix creates pathology. Thus, the instant compounds are useful for the treatment of osteoporosis, hyperparathyroidism, Paget's disease, hypercalcemia of malignancy, osteolytic lesions produced by bone metastasis, bone loss due to immobilization or sex hormone deficiency. The compounds of this invention are also believed to have utility as antitumor, anti-angiogenic,
30 antiinflammatory and anti-metastatic agents, and be useful in the treatment of atherosclerosis and restenosis.

The compound is administered either orally or parenterally to the patient, in a manner such that the concentration of drug is sufficient to inhibit bone resorption, or other such indication. The pharmaceutical composition containing the compound is administered
35 at an oral dose of between about 0.1 to about 50 mg/kg in a manner consistent with the condition of the patient. Preferably the oral dose would be about 0.5 to about 20 mg/kg. For acute therapy, parenteral administration is preferred. An intravenous infusion of the

peptide in 5% dextrose in water or normal saline, or a similar formulation with suitable excipients, is most effective, although an intramuscular bolus injection is also useful. Typically, the parenteral dose will be about 0.01 to about 100 mg/kg; preferably between 0.1 and 20 mg/kg. The compounds are administered one to four times daily at a level to achieve a total daily dose of about 0.4 to about 400 mg/kg/day. The precise level and method by which the compounds are administered is readily determined by one routinely skilled in the art by comparing the blood level of the agent to the concentration required to have a therapeutic effect.

This invention further provides a method for treating osteoporosis or inhibiting bone loss which comprises administering stepwise or in physical combination a compound of formula (I) and other inhibitors of bone resorption, such as bisphosphonates (i.e., allendronate), hormone replacement therapy, anti-estrogens, or calcitonin. In addition, this invention provides a method of treatment using a compound of this invention and an anabolic agent, such as the bone morphogenic protein, iproflavone, useful in the prevention of bone loss and/or to increase bone mass.

Additionally, this invention provides a method of inhibiting tumor growth which comprises administering stepwise or in physical combination a compound of formula (I) and an antineoplastic agent. Compounds of the camptothecin analog class, such as topotecan, irinotecan and 9-aminocamptothecin, and platinum coordination complexes, such as cisplatin, ormaplatin and tetraplatin, are well known groups of antineoplastic agents. Compounds of the camptothecin analog class are described in U.S. Patent Nos. 5,004,758, 4,604,463, 4,473,692, 4,545,880 4,342,776, 4,513,138, 4,399,276, EP Patent Application Publication Nos. 0 418 099 and 0 088 642, Wani, et al., *J. Med. Chem.*, **1986**, 29, 2358, Wani, et al., *J. Med. Chem.*, **1980**, 23, 554, Wani, et al., *J. Med. Chem.*, **1987**, 30, 1774, and Nitta, et al., *Proc. 14th International Congr. Chemotherapy.*, **1985**, *Anticancer Section I*, 28, the entire disclosure of each which is hereby incorporated by reference. The platinum coordination complex, cisplatin, is available under the name Platinol® from Bristol Myers-Squibb Corporation. Useful formulations for cisplatin are described in U.S. Patent Nos. 5,562,925 and 4,310,515, the entire disclosure of each which is hereby incorporated by reference.

In the method of inhibiting tumor growth which comprises administering stepwise or in physical combination a compound of formula (I) and an antineoplastic agent, the platinum coordination compound, for example cisplatin, can be administered using slow intravenous infusion. The preferred carrier is a dextrose/saline solution containing mannitol. The dose schedule of the platinum coordination compound may be on the basis of from about 1 to about 500 mg per square meter (mg/m^2) of body surface area per course of treatment. Infusions of the platinum coordination compound may be given one to two

times weekly, and the weekly treatments may be repeated several times. Using a compound of the camptothecin analog class in a parenteral administration, the course of therapy generally employed is from about 0.1 to about 300.0 mg/m² of body surface area per day for about five consecutive days. Most preferably, the course of therapy employed for topotecan is from about 1.0 to about 2.0 mg/m² of body surface area per day for about five consecutive days. Preferably, the course of therapy is repeated at least once at about a seven day to about a twenty-eight day interval.

The pharmaceutical composition may be formulated with both the compound of formula (I) and the antineoplastic agent in the same container, but formulation in different containers is preferred. When both agents are provided in solution form, they can be contained in an infusion/injection system for simultaneous administration or in a tandem arrangement.

For convenient administration of the compound of formula (I) and the antineoplastic agent at the same or different times, a kit is prepared, comprising, in a single container, such as a box, carton or other container, individual bottles, bags, vials or other containers each having an effective amount of the compound of formula (I) for parenteral administration, as described above, and an effective amount of the antineoplastic agent for parenteral administration, as described above. Such kit can comprise, for example, both pharmaceutical agents in separate containers or the same container, optionally as lyophilized plugs, and containers of solutions for reconstitution. A variation of this is to include the solution for reconstitution and the lyophilized plug in two chambers of a single container, which can be caused to admix prior to use. With such an arrangement, the antineoplastic agent and the compound of this invention may be packaged separately, as in two containers, or lyophilized together as a powder and provided in a single container.

When both agents are provided in solution form, they can be contained in an infusion/injection system for simultaneous administration or in a tandem arrangement. For example, the compound of formula (I) may be in an i.v. injectable form, or infusion bag linked in series, via tubing, to the antineoplastic agent in a second infusion bag. Using such a system, a patient can receive an initial bolus-type injection or infusion of the compound of formula (I) followed by an infusion of the antineoplastic agent.

The compounds may be tested in one of several biological assays to determine the concentration of compound which is required to have a given pharmacological effect.

Inhibition of vitronectin binding

Solid-Phase [³H]-SK&F-107260 Binding to $\alpha_v\beta_3$: Human placenta or human platelet $\alpha_v\beta_3$ (0.1-0.3 mg/mL) in buffer T (containing 2 mM CaCl₂ and 1% octylglucoside) was diluted with buffer T containing 1 mM CaCl₂, 1 mM MnCl₂, 1 mM MgCl₂ (buffer A) and

0.05% NaN₃, and then immediately added to 96-well ELISA plates (Corning, New York, NY) at 0.1 mL per well. 0.1 - 0.2 µg of α_vβ₃ was added per well. The plates were incubated overnight at 4°C. At the time of the experiment, the wells were washed once with buffer A and were incubated with 0.1 mL of 3.5% bovine serum albumin in the same
5 buffer for 1 hr at room temperature. Following incubation the wells were aspirated completely and washed twice with 0.2 mL buffer A.

Compounds were dissolved in 100% DMSO to give a 2 mM stock solution, which was diluted with binding buffer (15 mM Tris-HCl (pH 7.4), 100 mM NaCl, 1 mM CaCl₂, 1 mM MnCl₂, 1 mM MgCl₂) to a final compound concentration of 100 µM. This solution is
10 then diluted to the required final compound concentration. Various concentrations of unlabeled antagonists (0.001 - 100 µM) were added to the wells in triplicates, followed by the addition of 5.0 nM of [³H]-SK&F-107260 (65 - 86 Ci/mmol).

The plates were incubated for 1 hr at room temperature. Following incubation the wells were aspirated completely and washed once with 0.2 mL of ice cold buffer A in a
15 well-to-well fashion. The receptors were solubilized with 0.1 mL of 1% SDS and the bound [³H]-SK&F-107260 was determined by liquid scintillation counting with the addition of 3 mL Ready Safe in a Beckman LS Liquid Scintillation Counter, with 40% efficiency. Nonspecific binding of [³H]-SK&F-107260 was determined in the presence of 2 µM SK&F-107260 and was consistently less than 1% of total radioligand input. The
20 IC₅₀ (concentration of the antagonist to inhibit 50% binding of [³H]-SK&F-107260) was determined by a nonlinear, least squares curve-fitting routine, which was modified from the LUNDON-2 program. The K_i (dissociation constant of the antagonist) was calculated according to the equation: $K_i = IC_{50} / (1 + L/K_d)$, where L and K_d were the concentration and the dissociation constant of [³H]-SK&F-107260, respectively.

25 Compounds of the present invention inhibit vitronectin binding to SK&F 107260 in the concentration range of about 4.0 to about 0.0003 micromolar.

Compounds of this invention are also tested for *in vitro* and *in vivo* bone resorption in assays standard in the art for evaluating inhibition of bone formation, such as the pit
30 formation assay disclosed in EP 528 587, which may also be performed using human osteoclasts in place of rat osteoclasts, and the ovariectomized rat model, described by Wronski *et al.*, *Cells and Materials* **1991**, Sup. 1, 69-74.

Vascular smooth muscle cell migration assay

35 Rat or human aortic smooth muscle cells were used. The cell migration was monitored in a Transwell cell culture chamber by using a polycarbonate membrane with pores of 8 µm (Costar). The lower surface of the filter was coated with vitronectin. Cells

were suspended in DMEM supplemented with 0.2% bovine serum albumin at a concentration of $2.5 - 5.0 \times 10^6$ cells/mL, and were pretreated with test compound at various concentrations for 20 min at 20°C. The solvent alone was used as control. 0.2 mL of the cell suspension was placed in the upper compartment of the chamber. The lower
5 compartment contained 0.6 mL of DMEM supplemented with 0.2% bovine serum albumin. Incubation was carried out at 37°C in an atmosphere of 95% air/5% CO₂ for 24 hr. After incubation, the non-migrated cells on the upper surface of the filter were removed by gentle scraping. The filter was then fixed in methanol and stained with 10% Giemsa stain. Migration was measured either by a) counting the number of cells that had migrated to the
10 lower surface of the filter or by b) extracting the stained cells with 10% acetic acid followed by determining the absorbance at 600 nM.

Thyroparathyroidectomized rat model

Each experimental group consists of 5-6 adult male Sprague-Dawley rats (250-400g body
15 weight). The rats are thyroparathyroidectomized (by the vendor, Taconic Farms) 7 days prior to use. All rats receive a replacement dose of thyroxine every 3 days. On receipt of the rats, circulating ionized calcium levels are measured in whole blood immediately after it has been withdrawn by tail venipuncture into heparinized tubes. Rats are included if the ionized Ca level (measured with a Ciba-Corning model 634 calcium pH analyzer) is <1.2 mM/L. Each rat is fitted
20 with an indwelling venous and arterial catheter for the delivery of test material and for blood sampling respectively. The rats are then put on a diet of calcium-free chow and deionized water. Baseline Ca levels are measured and each rat is administered either control vehicle or human parathyroid hormone 1-34 peptide (hPTH1-34, dose 1.25 ug/kg/h in saline/0.1% bovine serum albumin, Bachem, Ca) or a mixture of hPTH1-34 and test material, by continuous intravenous
25 infusion via the venous catheter using an external syringe pump. The calcemic response of each rat is measured at two-hourly intervals during the infusion period of 6-8 hours.

Human osteoclast resorption and adhesion assays

Pit resorption and adhesion assays have been developed and standardized using
30 normal human osteoclasts derived from osteoclastoma tissue. Assay 1 was developed for the measurement of osteoclast pit volumes by laser confocal microscopy. Assay 2 was developed as a higher throughput screen in which collagen fragments (released during resorption) are measured by competitive ELISA.

35 Assay 1 (using laser confocal microscopy)

- Aliquots of human osteoclastoma-derived cell suspensions are removed from liquid nitrogen storage, warmed rapidly at 37°C and washed x1 in RPMI-1640 medium by centrifugation (1000rpm, 5 mins at 4°C).
- The medium is aspirated and replaced with murine anti-HLA-DR antibody then
5 diluted 1:3 in RPMI-1640 medium. The suspension is incubated for 30 mins on ice and mixed frequently.
- The cells are washed x2 with cold RPMI-1640 followed by centrifugation (1000 rpm, 5 mins at 4°C) and the cells are then transferred to a sterile 15 ml centrifuge tube. The number of mononuclear cells are enumerated in an improved Neubauer counting
10 chamber.
- Sufficient magnetic beads (5 / mononuclear cell), coated with goat anti-mouse IgG (Dynal, Great Neck, NY) are removed from their stock bottle and placed into 5 ml of fresh medium (this washes away the toxic azide preservative). The medium is removed by immobilizing the beads on a magnet and is replaced with fresh medium.
- The beads are mixed with the cells and the suspension is incubated for 30 mins on
15 ice. The suspension is mixed frequently.
- The bead-coated cells are immobilized on a magnet and the remaining cells (osteoclast-rich fraction) are decanted into a sterile 50 ml centrifuge tube.
- Fresh medium is added to the bead-coated cells to dislodge any trapped osteoclasts.
20 This wash process is repeated x10. The bead-coated cells are discarded.
- The viable osteoclasts are enumerated in a counting chamber, using fluorescein diacetate to label live cells. A large-bore disposable plastic pasteur pipet is used to add the sample to the chamber.
- The osteoclasts are pelleted by centrifugation and the density adjusted to the
25 appropriate number in EMEM medium (the number of osteoclasts is variable from tumor to tumor), supplemented with 10% fetal calf serum and 1.7g/liter of sodium bicarbonate.
- 3ml aliquots of the cell suspension (per compound treatment) are decanted into 15ml centrifuge tubes. The cells are pelleted by centrifugation.
- To each tube, 3ml of the appropriate compound treatment are added (diluted to 50
30 uM in the EMEM medium). Also included are appropriate vehicle controls, a positive control (anti-vitronectin receptor murine monoclonal antibody [87MEM1] diluted to 100 ug/ml) and an isotype control (IgG₂ diluted to 100 ug/ml). The samples are incubated at 37°C for 30 mins.
- 0.5ml aliquots of the cells are seeded onto sterile dentine slices in a 48-well plate
35 and incubated at 37°C for 2 hours. Each treatment is screened in quadruplicate.

- The slices are washed in six changes of warm PBS (10 ml / well in a 6-well plate) and then placed into fresh medium containing the compound treatment or control samples. The samples are incubated at 37°C for 48 hours.

5 *Tartrate resistant acid phosphatase (TRAP) procedure (selective stain for cells of the osteoclast lineage)*

- The bone slices containing the attached osteoclasts are washed in phosphate buffered saline and fixed in 2% glutaraldehyde (in 0.2M sodium cacodylate) for 5 mins.
- They are then washed in water and are incubated for 4 minutes in TRAP buffer at 10 37°C (0.5 mg/ml naphthol AS-BI phosphate dissolved in N,N-dimethylformamide and mixed with 0.25 M citrate buffer (pH 4.5), containing 10 mM sodium tartrate.
- Following a wash in cold water the slices are immersed in cold acetate buffer (0.1 M, pH 6.2) containing 1 mg/ml fast red garnet and incubated at 4°C for 4 minutes.
- Excess buffer is aspirated, and the slices are air dried following a wash in water.
- 15 • The TRAP positive osteoclasts (brick red/ purple precipitate) are enumerated by bright-field microscopy and are then removed from the surface of the dentine by sonication.
- Pit volumes are determined using the Nikon/LaserTec ILM21W confocal microscope.

20

Assay 2 (using an ELISA readout)

The human osteoclasts are enriched and prepared for compound screening as described in the initial 9 steps of Assay 1. For clarity, these steps are repeated hereinbelow.

- Aliquots of human osteoclastoma-derived cell suspensions are removed from liquid 25 nitrogen storage, warmed rapidly at 37°C and washed x1 in RPMI-1640 medium by centrifugation (1000rpm, 5 mins at 4°C).
- The medium is aspirated and replaced with murine anti-HLA-DR antibody then diluted 1:3 in RPMI-1640 medium. The suspension is incubated for 30 mins on ice and mixed frequently.
- 30 • The cells are washed x2 with cold RPMI-1640 followed by centrifugation (1000 rpm, 5 mins at 4°C) and the cells are then transferred to a sterile 15 ml centrifuge tube. The number of mononuclear cells are enumerated in an improved Neubauer counting chamber.
- Sufficient magnetic beads (5 / mononuclear cell), coated with goat anti-mouse IgG 35 (Dynal, Great Neck, NY) are removed from their stock bottle and placed into 5 ml of fresh medium (this washes away the toxic azide preservative). The medium is removed by immobilizing the beads on a magnet and is replaced with fresh medium.

- The beads are mixed with the cells and the suspension is incubated for 30 mins on ice. The suspension is mixed frequently.
- The bead-coated cells are immobilized on a magnet and the remaining cells (osteoclast-rich fraction) are decanted into a sterile 50 ml centrifuge tube.
- 5 • Fresh medium is added to the bead-coated cells to dislodge any trapped osteoclasts. This wash process is repeated x10. The bead-coated cells are discarded.
- The viable osteoclasts are enumerated in a counting chamber, using fluorescein diacetate to label live cells. A large-bore disposable plastic pasteur pipet is used to add the sample to the chamber.
- 10 • The osteoclasts are pelleted by centrifugation and the density adjusted to the appropriate number in EMEM medium (the number of osteoclasts is variable from tumor to tumor), supplemented with 10% fetal calf serum and 1.7g/liter of sodium bicarbonate.

In contrast to the method described above in Assay 1, the compounds are screened at 15 4 doses to obtain an IC_{50} , as outlined below:

- The osteoclast preparations are preincubated for 30 minutes at 37°C with test compound (4 doses) or controls.
- They are then seeded onto bovine cortical bone slices in wells of a 48-well tissue culture plate and are incubated for a further 2 hours at 37°C.
- 20 • The bone slices are washed in six changes of warm phosphate buffered saline (PBS), to remove non-adherent cells, and are then returned to wells of a 48 well plate containing fresh compound or controls.
- The tissue culture plate is then incubated for 48 hours at 37°C.
- The supernatants from each well are aspirated into individual tubes and are 25 screened in a competitive ELISA that detects the c-telopeptide of type I collagen which is released during the resorption process. This is a commercially available ELISA (Osteometer, Denmark) that contains a rabbit antibody that specifically reacts with an 8-amino acid sequence (Glu-Lys-Ala-His- Asp-Gly-Gly-Arg) that is present in the carboxy-terminal telopeptide of the $\alpha 1$ -chain of type I collagen. The results are 30 expressed as % inhibition of resorption compared to a vehicle control.

Human osteoclast adhesion assay

The human osteoclasts are enriched and prepared for compound screening as described above in the initial 9 steps of Assay 1. For clarity, these steps are repeated 35 hereinbelow.

- Aliquots of human osteoclastoma-derived cell suspensions are removed from liquid nitrogen storage, warmed rapidly at 37°C and washed x1 in RPMI-1640 medium by centrifugation (1000rpm, 5 mins at 4°C).
- The medium is aspirated and replaced with murine anti-HLA-DR antibody then
5 diluted 1:3 in RPMI-1640 medium. The suspension is incubated for 30 mins on ice and mixed frequently.
- The cells are washed x2 with cold RPMI-1640 followed by centrifugation (1000 rpm, 5 mins at 4°C) and the cells are then transferred to a sterile 15 ml centrifuge tube. The number of mononuclear cells are enumerated in an improved Neubauer counting
10 chamber.
- Sufficient magnetic beads (5 / mononuclear cell), coated with goat anti-mouse IgG (DynaI, Great Neck, NY) are removed from their stock bottle and placed into 5 ml of fresh medium (this washes away the toxic azide preservative). The medium is removed by immobilizing the beads on a magnet and is replaced with fresh medium.
- The beads are mixed with the cells and the suspension is incubated for 30 mins on
15 ice. The suspension is mixed frequently.
- The bead-coated cells are immobilized on a magnet and the remaining cells (osteoclast-rich fraction) are decanted into a sterile 50 ml centrifuge tube.
- Fresh medium is added to the bead-coated cells to dislodge any trapped osteoclasts.
20 This wash process is repeated x10. The bead-coated cells are discarded.
- The viable osteoclasts are enumerated in a counting chamber, using fluorescein diacetate to label live cells. A large-bore disposable plastic pasteur pipet is used to add the sample to the chamber.
- The osteoclasts are pelleted by centrifugation and the density adjusted to the
25 appropriate number in EMEM medium (the number of osteoclasts is variable from tumor to tumor), supplemented with 10% fetal calf serum and 1.7g/liter of sodium bicarbonate.
- Osteoclastoma-derived osteoclasts are preincubated with compound (4 doses) or controls at 37°C for 30 minutes.
- The cells are then seeded onto osteopontin-coated slides (human or rat osteopontin,
30 2.5ug/ml) and incubated for 2 hours at 37°C.
- Non adherent cells are removed by washing the slides vigorously in phosphate buffered saline and the cells remaining on the slides are fixed in acetone.
- The osteoclasts are stained for tartrate-resistant acid phosphatase (TRAP), a
35 selective marker for cells of this phenotype (see steps 15 -17), and are enumerated by light microscopy. The results are expressed as % inhibition of adhesion compared to a vehicle control.

Cell Adhesion Assay

Cells and Cell Culture

Human embryonic kidney cells (HEK293 cells) were obtained from ATCC (Catalog No. CRL 1573). Cells were grown in Earl's minimal essential medium (EMEM) medium containing Earl's salts, 10% fetal bovine serum, 1% glutamine and 1% Penicillin-
5 Steptomycin.

Constructs and Transfections

A 3.2 kb EcoRI-KpnI fragment of the α_v subunit and a 2.4 kb XbaI- XhoI fragment of the β_3 subunit were inserted into the EcoRI - EcoRV cloning sites of the pCDN vector
10 (Aiyar et al., 1994) which contains a CMV promoter and a G418 selectable marker by blunt end ligation. For stable expression, 80×10^6 HEK 293 cells were electrotransformed with $\alpha_v + \beta_3$ constructs (20 μ g DNA of each subunit) using a Gene Pulser (Hensley et al., 1994) and plated in 100 mm plates (5×10^5 cells/plate). After 48 hr, the growth medium was supplemented with 450 μ g/mL Geneticin (G418 Sulfate, GIBCO-BRL, Bethesda, MD).
15 The cells were maintained in selection medium until the colonies were large enough to be assayed.

Immunocytochemical analysis of transfected cells

To determine whether the HEK 293 transfectants expressed the vitronectin receptor, the cells were immobilized on glass microscope slides by centrifugation, fixed in
20 acetone for 2 min at room temperature and air dried. Specific reactivity with 23C6, a monoclonal antibody specific for the $\alpha_v \beta_3$ complex was demonstrated using a standard indirect immunofluorescence method.

Cell Adhesion Studies

25 Corning 96-well ELISA plates were precoated overnight at 4°C with 0.1 mL of human vitronectin (0.2 μ g/mL in RPMI medium). At the time of the experiment, the plates were washed once with RPMI medium and blocked with 3.5% BSA in RPMI medium for 1 hr at room temperature. Transfected 293 cells were resuspended in RPMI medium, supplemented with 20 mM Hepes, pH 7.4 and 0.1% BSA at a density of 0.5×10^6 cells/mL.
30 0.1 mL of cell suspension was added to each well and incubated for 1 hr at 37°C, in the presence or absence of various $\alpha_v \beta_3$ antagonists. Following incubation, 0.025 mL of a 10% formaldehyde solution, pH 7.4, was added and the cells were fixed at room temperature for 10 min. The plates were washed 3 times with 0.2 mL of RPMI medium and the adherent cells were stained with 0.1 mL of 0.5% toluidine blue for 20 min at room

temperature. Excess stain was removed by extensive washing with deionized water. The toluidine blue incorporated into cells was eluted by the addition of 0.1 mL of 50% ethanol containing 50 mM HCl. Cell adhesion was quantitated at an optical density of 600 nm on a microtiter plate reader (Titertek Multiskan MC, Sterling, VA).

5

Solid-Phase $\alpha_v\beta_3$ Binding Assay:

The vitronectin receptor $\alpha_v\beta_3$ was purified from human placenta. Receptor preparation was diluted with 50 mM Tris-HCl, pH 7.5, 100 mM NaCl, 1 mM CaCl_2 , 1 mM MnCl_2 , 1 mM MgCl_2 (buffer A) and was immediately added to 96-well ELISA plates at 0.1 ml per well. 0.1-0.2 μg of $\alpha_v\beta_3$ was added per well. The plates were incubated overnight at 4°C. At the time of the experiment, the wells were washed once with buffer A and were incubated with 0.1 ml of 3.5% bovine serum albumin in the same buffer for 1 hr at room temperature. Following incubation the wells were aspirated completely and washed twice with 0.2 ml buffer A.

15 In a [^3H]-SK&F-107260 competition assay, various concentrations of unlabeled antagonists (0.001-100 μM) were added to the wells, followed by the addition of 5.0 nM of [^3H]-SK&F-107260. The plates were incubated for 1 hr at room temperature. Following incubation the wells were aspirated completely and washed once with 0.2 ml of ice cold buffer A in a well-to-well fashion. The receptors were solubilized with 0.1 ml of 1% SDS and the bound [^3H]-SK&F-107260 was determined by liquid scintillation counting with the addition of 3 ml Ready Safe in a Beckman LS 6800 Liquid Scintillation Counter, with 40% efficiency. Nonspecific binding of [^3H]-SK&F-107260 was determined in the presence of 2 μM SK&F-107260 and was consistently less than 1% of total radioligand input. The IC_{50} (concentration of the antagonist to inhibit 50% binding of [^3H]-SK&F-107260) was determined by a nonlinear, least squares curve-fitting routine, which was modified from the LUNDON-2 program. The K_i (dissociation constant of the antagonist) was calculated according to Cheng and Prusoff equation: $K_i = \text{IC}_{50} / (1 + L/K_d)$, where L and K_d were the concentration and the dissociation constant of [^3H]-SK&F-107260, respectively.

30

Inhibition of RGD-mediated GPIIb-IIIa binding

Purification of GPIIb-IIIa

Ten units of outdated, washed human platelets (obtained from Red Cross) were lysed by gentle stirring in 3% octylglucoside, 20 mM Tris-HCl, pH 7.4, 140 mM NaCl, 2 mM CaCl_2 at 4°C for 2 h. The lysate was centrifuged at 100,000g for 1 h. The supernatant obtained was applied to a 5 mL lentil lectin sepharose 4B column (E.Y. Labs) preequilibrated with 20 mM Tris-HCl, pH 7.4, 100 mM NaCl, 2 mM CaCl_2 , 1%

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octylglucoside (buffer A). After 2 h incubation, the column was washed with 50 mL cold buffer A. The lectin-retained GPIIb-IIIa was eluted with buffer A containing 10% dextrose. All procedures were performed at 4°C. The GPIIb-IIIa obtained was >95% pure as shown by SDS polyacrylamide gel electrophoresis.

5

Incorporation of GPIIb-IIIa in Liposomes.

A mixture of phosphatidylserine (70%) and phosphatidylcholine (30%) (Avanti Polar Lipids) were dried to the walls of a glass tube under a stream of nitrogen. Purified GPIIb-IIIa was diluted to a final concentration of 0.5 mg/mL and mixed with the
10 phospholipids in a protein:phospholipid ratio of 1:3 (w:w). The mixture was resuspended and sonicated in a bath sonicator for 5 min. The mixture was then dialyzed overnight using 12,000-14,000 molecular weight cutoff dialysis tubing against a 1000-fold excess of 50 mM Tris-HCl, pH 7.4, 100 mM NaCl, 2 mM CaCl₂ (with 2 changes). The GPIIb-IIIa-containing liposomes were centrifuged at 12,000g for 15 min and resuspended in the dialysis
15 buffer at a final protein concentration of approximately 1 mg/mL. The liposomes were stored at -70°C until needed.

Competitive Binding to GPIIb-IIIa

The binding to the fibrinogen receptor (GPIIb-IIIa) was assayed by an indirect
20 competitive binding method using [³H]-SK&F-107260 as an RGD-type ligand. The binding assay was performed in a 96-well filtration plate assembly (Millipore Corporation, Bedford, MA) using 0.22 µm hydrophilic durapore membranes. The wells were precoated with 0.2 mL of 10 µg/mL polylysine (Sigma Chemical Co., St. Louis, MO.) at room temperature for 1 h to block nonspecific binding. Various concentrations of unlabeled
25 benzazepines were added to the wells in quadruplicate. [³H]-SK&F-107260 was applied to each well at a final concentration of 4.5 nM, followed by the addition of 1 µg of the purified platelet GPIIb-IIIa-containing liposomes. The mixtures were incubated for 1 h at room temperature. The GPIIb-IIIa-bound [³H]-SK&F-107260 was separated from the unbound by filtration using a Millipore filtration manifold, followed by washing with ice-cold buffer
30 (2 times, each 0.2 mL). Bound radioactivity remaining on the filters was counted in 1.5 mL Ready Solve (Beckman Instruments, Fullerton, CA) in a Beckman Liquid Scintillation Counter (Model LS6800), with 40% efficiency. Nonspecific binding was determined in the presence of 2 µM unlabeled SK&F-107260 and was consistently less than 0.14% of the total radioactivity added to the samples. All data points are the mean of quadruplicate
35 determinations.

Competition binding data were analyzed by a nonlinear least-squares curve fitting procedure. This method provides the IC₅₀ of the antagonists (concentration of the

antagonist which inhibits specific binding of [³H]-SK&F-107260 by 50% at equilibrium). The IC₅₀ is related to the equilibrium dissociation constant (K_i) of the antagonist based on the Cheng and Prusoff equation: $K_i = IC_{50}/(1+L/K_d)$, where L is the concentration of [³H]-SK&F-107260 used in the competitive binding assay (4.5 nM), and K_d is the dissociation constant of [³H]-SK&F-107260 which is 4.5 nM as determined by Scatchard analysis.

Preferred compounds of this invention have an affinity for the vitronectin receptor relative to the fibrinogen receptor of greater than 10:1. Most preferred compounds have a ratio of activity of greater than 100:1.

The efficacy of the compounds of formula (I) alone or in combination with an antineoplastic agent may be determined using several transplantable mouse tumor models. See U. S. Patent Nos. 5,004,758 and 5,633,016 for details of these models

The examples which follow are intended in no way to limit the scope of this invention, but are provided to illustrate how to make and use the compounds of this invention. Many other embodiments will be readily apparent to those skilled in the art.

EXAMPLES

General

- 5 ¹H nuclear magnetic resonance (NMR) spectra were recorded at either 250 or 400 MHz. Chemical shifts are reported in parts per million (δ) downfield from the internal standard tetramethylsilane (TMS). Abbreviations for NMR data are as follows: s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet, dd=doublet of doublets, dt=doublet of triplets, app=apparent, br=broad. J indicates the NMR coupling constant measured in Hertz.
- 10 CDCl₃ is deuteriochloroform, DMSO-d₆ is hexadeuteriodimethylsulfoxide, and CD₃OD is tetradeuteriomethanol. Infrared (IR) spectra were recorded in transmission mode, and band positions are reported in inverse wavenumbers (cm⁻¹). Mass spectra were obtained using electrospray (ES) or FAB ionization techniques. Elemental analyses were performed either in-house or by Quantitative Technologies Inc., Whitehouse, NJ. Melting points were taken
- 15 on a Thomas-Hoover melting point apparatus and are uncorrected. All temperatures are reported in degrees Celsius. Analtech Silica Gel GF and E. Merck Silica Gel 60 F-254 thin layer plates were used for thin layer chromatography. Both flash and gravity chromatography were carried out on E. Merck Kieselgel 60 (230-400 mesh) silica gel. Analytical and preparative HPLC were carried out on Rainin or Beckman chromatographs.
- 20 ODS refers to an octadecylsilyl derivatized silica gel chromatographic support. 5 μ Apex-ODS indicates an octadecylsilyl derivatized silica gel chromatographic support having a nominal particle size of 5 μ, made by Jones Chromatography, Littleton, Colorado. YMC ODS-AQ® is an ODS chromatographic support and is a registered trademark of YMC Co. Ltd., Kyoto, Japan. PRP-1® is a polymeric (styrene-divinylbenzene) chromatographic
- 25 support, and is a registered trademark of Hamilton Co., Reno, Nevada. Celite® is a filter aid composed of acid-washed diatomaceous silica, and is a registered trademark of Manville Corp., Denver, Colorado.

Preparation IPreparation of methyl (\pm)-8-hydroxy-3-oxo-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetate

5 a) 4-Bromo-3-bromomethylanisole

A mixture of 2-bromo-5-methoxytoluene (20 g, 0.10 mol), N-bromosuccinimide (19.6 g, 0.11 mol), benzoyl peroxide (1 g, 4 mmol), and methylene chloride (200 mL) was irradiated for 18 hr with a flood lamp to effect gentle reflux. The mixture was then cooled to -10°C for several hours and the solution was decanted away from the precipitated
10 succinimide. The solution was concentrated and the residue was crystallized from chloroform/hexane to give the title compound (19.7 g, 70%) as pale yellow prisms: ^1H NMR (CDCl_3) δ 7.45 (d, J = 8.9 Hz, 1 H), 6.99 (d, J = 3 Hz, 1 H), 6.74 (dd, J = 8.9, 3 Hz, 1 H), 4.55 (s, 2 H) 3.80 (s, 3 H).

15 b) 3-Bis(*tert*-butoxycarbonyl)aminomethyl-4-bromoanisole

A mixture of 4-bromo-3-bromomethylanisole (24 g, 86 mmol) and potassium di-*tert*-butyl iminodicarboxylate (24 g, 94 mmol) in dimethylformamide (200 mL) was stirred under argon at room temperature for 18 hr. The reaction was then concentrated under vacuum and the residue was partitioned between ethyl acetate and water. The organic
20 phase was washed with water and brine, dried (MgSO_4), and concentrated. The residue was recrystallized from hexane to give the title compound (15 g, 42%) as a white solid: ^1H NMR (CDCl_3) δ 7.40 (d, J = 8.6 Hz, 1 H), 6.68 (m, 2 H), 4.81 (s, 2 H), 3.74 (s, 3 H), 1.44 (s, 18 H).

25 c) Methyl (\pm)-3-carbomethoxy-4-[2-bis(*tert*-butoxycarbonyl)aminomethyl-4-methoxyphenyl]-3-butenate

A 500 mL flask was charged with 3-bis(*tert*-butoxycarbonyl)aminomethyl-4-bromoanisole (15 g, 36 mmol), dimethyl itaconate (7.5 g, 47 mmol), tri-*o*-tolylphosphine (1 g, 3 mol), palladium acetate (0.4 g, 2 mmol), diisopropylethylamine (12.8 mL, 72 mmol),
30 and propionitrile (150 mL). The mixture was purged with argon (several evacuation/argon flush cycles), then was heated to reflux under argon for 1 hr. The reaction was allowed to cool to RT, then was poured into ice-cold ethyl ether (500 mL). The resulting precipitate was removed by filtration and the filtrate was concentrated. The residue was purified by chromatography on silica gel (10% - 20% ethyl acetate in hexane) to give the title
35 compound (11.8 g, 66%) as a pale yellow oil: ^1H NMR (CDCl_3) δ 7.94 (s, 1 H), 7.15 (d, J = 8.1 Hz, 1 H), 6.77 (d, J = 8.1 Hz, 1 H), 6.76 (s, 1 H), 4.73 (s, 2 H), 3.81 (s, 3 H), 3.79 (s, 3 H), 3.71 (s, 3 H), 3.38 (s, 2 H), 1.45 (s, 18 H).

d) Methyl (±)-3-carbomethoxy-4-[2-bis(*tert*-butoxycarbonyl)aminomethyl-4-methoxyphenyl]butanoate

A pressure vessel charged with methyl (±)-3-carbomethoxy-4-[2-bis(*tert*-
5 butoxycarbonyl)aminomethyl-4-methoxyphenyl]-3-butenolate (11.8 g), ethyl acetate (120 mL), and 10% palladium on charcoal (1 g) was shaken under 45 psi of hydrogen for 18 hr. The mixture was then filtered and the filtrate was concentrated to give the title compound (12 g, 100%) as a colorless oil: ¹H NMR (CDCl₃) δ 7.00 (d, J = 8.2 Hz, 1 H), 6.71 (m, 2 H), 4.81 (s, 2 H), 3.75 (s, 3 H), 3.66 (s, 3 H), 3.63 (s, 3 H), 3.05 (m, 2 H), 2.73 (m, 2 H),
10 2.42 (dd, J = 16.0, 4.8 Hz, 1 H), 1.44 (s, 18 H).

e) Methyl (±)-3-carbomethoxy-4-[2-(aminomethyl)-4-methoxyphenyl]butanoate

A solution of methyl (±)-3-carbomethoxy-4-[2-bis(*tert*-
butoxycarbonyl)aminomethyl-4-methoxyphenyl]butanoate (12 g) in chloroform (100 mL)
15 and trifluoroacetic acid (50 mL) was stirred under argon at room temperature for 4 hr. The solution was then concentrated under vacuum to give the title compound (10 g, 100%) as a viscous oil: MS (ES) m/e 296.2 (M + H)⁺.

f) Methyl (±)-8-methoxy-3-oxo-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetate

A solution of methyl (±)-3-carbomethoxy-4-[2-(aminomethyl)-4-
20 methoxyphenyl]butanoate (10 g, 24 mmol) and triethylamine (17 mL, 120 mmol) in toluene (100 mL) was heated at reflux for 18 hr. The reaction was then concentrated and the residue was partitioned between ethyl acetate and water. The aqueous layer was extracted twice with ethyl acetate and the combined organic extracts were washed with brine, dried
25 (MgSO₄), and concentrated to afford the title compound (4.8 g, 76%) as tan solid: MS (ES) m/e 264.2 (M + H)⁺.

g) Methyl (±)-8-hydroxy-3-oxo-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetate

Anhydrous aluminum chloride (7.6 g, 57 mmol) was added portionwise to a stirred
30 solution of methyl (±)-8-methoxy-3-oxo-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetate (3.0 g, 11 mmol) and ethanethiol (4.2 mL, 57 mmol) in methylene chloride (100 mL) at 0°C under argon. The resulting mixture was allowed to warm to room temperature and stir overnight, then was concentrated. The residue was triturated with ice-water, and the resulting solid was collected by filtration and dried to give the title compound (2.64 g,
35 91%) as an off-white solid: MS (ES) m/e 250.2 (M + H)⁺.

Preparation 2Preparation of methyl (\pm)-8-hydroxy-2-methyl-3-oxo-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetate

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a) 3-[N-(*tert*-Butoxycarbonyl)-N-methylamino]methyl-4-bromoanisole

40% aqueous methylamine (49 mL, 563 mmole) was added rapidly to a solution of 4-bromo-3-bromomethylanisole (15.76 g, 56.29 mmole) in THF (280 mL) at RT. After 2.5 hr, the reaction was concentrated, and the residue was partitioned between Et₂O (560 mL) and 1.0 N NaOH (100 mL). The layers were separated, and the organic layer was dried (MgSO₄) and concentrated to a yellow oil: TLC (5% MeOH/CHCl₃) R_f 0.32.

The oil was dissolved in CHCl₃ (280 mL), and di-*tert*-butyl dicarbonate (1.29 g, 56.29 mmole) was added. The reaction was stirred at RT for 45 min, then was concentrated. Silica gel chromatography (5% EtOAc/toluene) gave the title compound (16.81 g, 90%) as a light yellow oil: TLC (5% EtOAc/toluene) R_f 0.43; ¹H NMR (400, CDCl₃) mixture of rotamers; δ 7.42 (d, J = 8.7 Hz, 1 H), 6.65 - 6.80 (m, 2 H), 4.40 - 4.55 (m, 2 H), 3.77 (s, 3 H), 2.81 - 2.97 (m, 3 H), 1.37 - 1.60 (m, 9 H); MS (ES) m/e 352/354 (M + Na)⁺.

b) Methyl (\pm)-3-carbomethoxy-4-[2-[N-(*tert*-butoxycarbonyl)-N-methylamino]methyl-4-methoxyphenyl]butanoate

A solution of 3-[N-(*tert*-butoxycarbonyl)-N-methylamino]methyl-4-bromoanisole (4.95 g, 15 mmol), dimethyl itaconate (3.08 g, 19.5 mmol), palladium acetate (168 mg, 0.75 mmol), tri-*o*-tolylphosphine (457 mg, 1.5 mol), and diisopropylethylamine (5.2 mL, 30 mmol) in propionitrile (75 mL) was heated to reflux for 45 min, then was concentrated on the rotavap. The residue was diluted with Et₂O (150 mL), and the mixture was filtered through celite® to remove insoluble materials. The filtrate was concentrated, and the residue was reconcentrated from xylenes. Chromatography on silica gel (gradient: 20% EtOAc/hexanes, then 1:1 EtOAc/hexanes) removed the phosphine and baseline materials; all other materials with R_f 0.40 - 0.70 were collected together and concentrated to leave a cloudy, yellow oil: TLC (30% EtOAc/hexanes) R_f 0.41 (major product).

The oil was dissolved in MeOH (75 mL), and 10% Pd/C was added carefully. The mixture was shaken under hydrogen (50 psi) for 2.5 hr, then was filtered through celite® to remove the catalyst. The filtrate was concentrated, and the residue was resubmitted to the reaction conditions. After another 2.5 hr, the mixture was filtered through celite® to remove the catalyst, and the filtrate was concentrated to leave a light yellow oil. This was reconcentrated from CHCl₃/hexanes, then was chromatographed on silica gel (gradient:

20% EtOAc/hexanes, then 1:1 EtOAc/hexanes) to afford the title compound (4.53 g, 74%) as a light yellow oil: TLC (30% EtOAc/toluene) R_f 0.46; ^1H NMR (400, CDCl_3) mixture of rotamers; δ 7.03 (d, J = 8.2 Hz, 1 H), 6.65 - 6.80 (m, 2 H), 4.46 (br s, 2 H), 3.77 (s, 3 H), 3.64 (s, 3 H), 3.63 (s, 3 H), 2.62 - 3.12 (m, 7 H), 2.35 - 2.50 (m, 1 H), 1.47 (br s, 9 H); MS (ES) m/e 432 ($M + \text{Na}$) $^+$.

c) Methyl (\pm)-3-carbomethoxy-4-[2-(methylamino)methyl-4-methoxyphenyl]butanoate

TFA (55 mL) was added all at once to a solution of methyl (\pm)-3-carbomethoxy-4-[2-[N-(*tert*-butoxycarbonyl)-N-methylamino]methyl-4-methoxyphenyl]butanoate (4.53 g, 11.06 mmole) in anhydrous CH_2Cl_2 (55 mL) at 0°C , and the reaction was warmed to RT. After 1 hr, the reaction was concentrated, and the residue was reconcentrated from toluene (2 x 100 mL) to leave the title compound (11.06 mmole, quantitative) as a light yellow oil: MS (ES) m/e 310 ($M + \text{H}$) $^+$.

d) Methyl (\pm)-8-methoxy-2-methyl-3-oxo-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetate

A solution of methyl (\pm)-3-carbomethoxy-4-[2-(methylamino)methyl-4-methoxyphenyl]butanoate (11.06 mmole) and diisopropylethylamine (5.8 mL, 33.18 mmole) in toluene (110 mL) was heated at reflux for 25 hr, stirred at RT for 4 days, then heated at reflux for another 24 hr. Concentration and silica gel chromatography (5% MeOH in 1:1 EtOAc/ CHCl_3) gave the title compound (2.88 g, 94%) as a light yellow solid: TLC (5% MeOH in 1:1 EtOAc/ CHCl_3) R_f 0.63; ^1H NMR (250, CDCl_3) δ 7.02 (d, J = 8.4 Hz, 1 H), 6.78 (dd, J = 8.4, 2.7 Hz, 1 H), 6.63 (d, J = 2.7 Hz, 1 H), 5.29 (d, J = 16.3 Hz, 1 H), 3.50 - 3.90 (m, 2 H), 3.79 (s, 3 H), 3.71 (s, 3 H), 2.73 - 3.16 (m, 3 H), 3.04 (s, 3 H), 2.41 (dd, J = 16.7, 5.4 Hz, 1 H); MS (ES) m/e 300 ($M + \text{Na}$) $^+$, 278 ($M + \text{H}$) $^+$.

e) Methyl (\pm)-8-hydroxy-2-methyl-3-oxo-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetate

Anhydrous aluminum chloride (1.35 g, 10.15 mmole) was added all at once to a solution of methyl (\pm)-8-methoxy-2-methyl-3-oxo-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetate (562 mg, 2.03 mmole) and ethanethiol (0.75 mL, 10.15 mmole) in anhydrous CH_2Cl_2 (20 mL) at 0°C under argon. The mixture was warmed to RT and stirred for 4.5 hr, then was recooled to 0°C . Ice cold H_2O (20 mL) was added, and the mixture was stirred briskly for 5 min, then was extracted with CHCl_3 (3 x 20 mL). The combined CHCl_3 layers were dried (MgSO_4) and concentrated to leave a residue. The aqueous layer was suction filtered to collect a solid precipitate. This precipitate and the residue from the CHCl_3 layer were combined in 1:1 MeOH/ CHCl_3 , and the solution was concentrated to leave an off-white solid. This was triturated with hot MeOH, and the mixture was allowed to cool to RT. The solid was collected by suction filtration and washed sequentially with

cold MeOH and Et₂O. Drying in high vacuum at 40°C gave the title compound (467.9 mg, 88%) as a colorless solid: TLC (5% MeOH/CHCl₃) R_f 0.17; ¹H NMR (250, DMSO-d₆) δ 9.29(s, 1 H), 6.89 (d, J = 8.1 Hz, 1 H), 6.50 - 6.70 (m, 2 H), 5.16 (d, J = 16.4 Hz, 1 H), 3.84 (d, J = 16.4 Hz, 1 H), 3.60 - 3.85 (m, 1 H), 3.56 (s, 3 H), 2.30 - 3.00 (m, 4 H), 2.86 (s, 3 H);
5 MS (ES) m/e 286 (M + Na)⁺, 264 (M + H)⁺.

Preparation 3

Preparation of 2-[(3-hydroxy-1-propyl)amino]pyridine-N-oxide

10

a) 2-[(3-Hydroxy-1-propyl)amino]pyridine-N-oxide

A mixture of 2-chloropyridine-N-oxide (16.6 g, 0.1 mole), 3-amino-1-propanol (15.3 mL, 0.2 mole), NaHCO₃ (42 g, 0.5 mole), and *tert*-amyl alcohol (100 mL) was heated to reflux. After 21 hr, the reaction was cooled, diluted with CH₂Cl₂ (300 mL), and suction
15 filtered to remove insoluble materials. The filtrate was concentrated and reconstituted from toluene to leave a yellow oil. Silica gel chromatography (20% MeOH/CHCl₃) gave the title compound (15.62 g, 93%) as a yellow solid: TLC (20% MeOH/CHCl₃) R_f 0.48; ¹H NMR (250, CDCl₃) δ 8.07 (dd, J = 6.6, 1.2 Hz, 1 H), 7.34 (br t, 1 H), 7.10 - 7.30 (m, 1 H), 6.64 (dd, J = 8.5, 1.4 Hz, 1 H), 6.40 - 6.60 (m, 1 H), 4.49 (br s, 1 H), 3.65 - 3.90 (m, 2 H), 3.35 - 3.60 (m, 2 H), 1.75 - 2.00 (m, 2 H); MS (ES) m/e 169 (M + H)⁺.
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Preparation 4

Preparation of 2-[(3-hydroxy-1-propyl)amino]-4-nitropyridine-N-oxide

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a) 2-[(3-Hydroxy-1-propyl)amino]-4-nitropyridine-N-oxide

According to the procedure of Preparation 3, except substituting 2-chloro-4-nitropyridine-N-oxide (see Jain, P. C.; Chatterjee, S. K.; Anand, N. *Indian Journal of Chemistry* 1966, 403) for the 2-chloropyridine-N-oxide hydrochloride, the title compound
30 was prepared as an orange solid: MS (ES) m/e 214.2 (M + H)⁺.

Preparation 5Preparation of 2-[(3-hydroxy-1-propyl)amino]-4-methoxypyridine-N-oxide

5 a) 2-[(3-Hydroxy-1-propyl)amino]-4-methoxypyridine-N-oxide

A solution of 2-[(3-hydroxy-1-propyl)amino]-4-nitropyridine-N-oxide (0.275 g, 1 mmol) and 0.5 M NaOMe in MeOH (16 mL, 8 mmol) was heated at reflux under argon for 3 hr. The reaction was then allowed to cool, and glacial AcOH (0.5 mL, 8 mmol) was added. The solution was concentrated to dryness and the residue was triturated with 10 CH₂Cl₂. The insoluble materials were removed by filtration and the filtrate was concentrated. Silica gel chromatography (5 - 15% MeOH/ CH₂Cl₂) gave the title compound (0.23 g, 90%) as a colorless oil: MS (ES) m/e 199.0 (M + H)⁺.

Preparation 6

15

Preparation of (±)-8-hydroxy-3-oxo-2-(2,2,2-trifluoroethyl)-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetate20 a) 3-[N-(*tert*-Butoxycarbonyl)-N-(2,2,2-trifluoroethyl)amino]methyl-4-bromoanisole

2,2,2-Trifluoroethylamine (4.9 mL, 62.5 mmole) was added rapidly to a solution of 4-bromo-3-bromomethylanisole (7.00 g, 25 mmole) in anhydrous DMSO (25 mL) at RT. The reaction warmed to approximately 30 - 35 °C. After 2 hr, the reaction was diluted with ice-cold 0.5 N NaOH (100 mL) and extracted with Et₂O (3 x 100 mL). The combined Et₂O layers were washed sequentially with H₂O (2 x 25 mL) and brine (25 mL), dried 25 (MgSO₄), and concentrated to a light yellow oil: TLC (toluene) R_f 0.43.

The oil was dissolved in anhydrous CH₂Cl₂ (48 mL) in a roundbottom flask, and di-*tert*-butyl dicarbonate (10.48 g, 48.04 mmole) was added. The flask containing the reaction solution was placed on the rotavap and rotated in vacuum at 50 °C for 16 hr. The resulting residue was diluted with hexanes (100 mL) and the solution was seeded with a 30 small amount of the pure, solid product (obtained from a previous experiment by silica gel chromatography using 10% EtOAc/hexanes as eluent). The mixture was allowed to stand at RT for several hr, then was placed in the refrigerator overnight. The product was collected by suction filtration and washed with hexanes. Drying in vacuum gave the title compound (7.19 g, 75%) as a colorless solid. The mother liquors were concentrated and 35 chromatographed on silica gel (10% EtOAc/hexanes) to afford additional title compound (1.42 g; total = 8.61 g, 90%): TLC (10% EtOAc/toluene) R_f 0.48; mp 86 - 89 °C; ¹H NMR

(250, CDCl₃) δ 7.44 (d, J = 9.0 Hz, 1 H), 6.64 - 6.82 (m, 2 H), 4.52 - 4.70 (m, 2 H), 3.61 - 4.00 (m, 2 H), 3.77 (s, 3 H), 1.22 - 1.68 (m, 9 H).

- b) Methyl (\pm)-3-carbomethoxy-4-[2-[N-(*tert*-butoxycarbonyl)-N-(2,2,2-trifluoroethyl)amino]methyl-4-methoxyphenyl]butanoate

A solution of 3-[N-(*tert*-butoxycarbonyl)-N-(2,2,2-trifluoroethyl)amino]methyl-4-bromoanisole (9.17 g, 23.03 mmol), dimethyl itaconate (4.73 g, 29.94 mmol), palladium acetate (259 mg, 1.15 mmol), tri-*o*-tolylphosphine (701 mg, 2.30 mol), and diisopropylethylamine (8.0 mL, 46.06 mmol) in propionitrile (115 mL) was deoxygenated (3x evacuation/argon purge cycles), then was heated to reflux under argon. After 2 hr the reaction was concentrated and reconstituted from toluene. Silica gel chromatography (30% EtOAc/hexanes, load sample with CH₂Cl₂) removed the phosphine and baseline materials; all other materials with R_f 0.55 - 0.70 were collected together and concentrated to leave a yellow oil. This was taken up in 20% EtOAc/hexanes (200 mL) and allowed to stand at RT for 1 hr then in the refrigerator overnight. The mixture was filtered to remove a yellow precipitate, and the filtrate was concentrated to leave 9.93 g (91%) of a yellow oil: TLC (30% EtOAc/hexanes) R_f 0.55 (major product).

The oil was dissolved in EtOAc (100 mL), and 10% Pd/C (4.44 g, 4.18 mmole) was added. The mixture was shaken under hydrogen (50 psi) for 3.5 hr, then was filtered through celite® to remove the catalyst. The filtrate was concentrated, and the residue was chromatographed on silica gel (gradient: 20% EtOAc/hexanes) to afford the title compound (7.98 g, 73% for two steps) as a colorless oil: TLC (20% EtOAc/toluene) R_f 0.35; ¹H NMR (250, CDCl₃) δ 7.05 (d, J = 8.4 Hz, 1 H), 6.76 (dd, J = 8.4, 2.7 Hz, 1 H), 6.60 - 6.72 (m, 1 H), 4.50 - 4.80 (m, 2 H), 3.45 - 3.95 (m, 2 H), 3.77 (s, 3 H), 3.63 (s, 6 H), 2.85 - 3.09 (m, 2 H), 2.58 - 2.80 (m, 2 H), 2.33 - 2.50 (m, 1 H), 1.20 - 1.70 (m, 9 H); MS (ES) m/e 500 (M + Na)⁺.

- c) Methyl (\pm)-3-carbomethoxy-4-[2-(2,2,2-trifluoroethylamino)methyl-4-methoxyphenyl]butanoate

TFA (55 mL) was added all at once to a solution of methyl (\pm)-3-carbomethoxy-4-[2-[N-(*tert*-butoxycarbonyl)-N-(2,2,2-trifluoroethyl)amino]methyl-4-methoxyphenyl]butanoate (7.98 g, 16.71 mmole) in anhydrous CH₂Cl₂ (42 mL) at 0°C under argon, and the reaction was warmed to RT. After 1.5 hr, the reaction was concentrated, and the residue was reconstituted from xylenes. Drying in high vacuum at 40 °C left the title compound (8.70 g, quantitative) as a yellow solid: MS (ES) m/e 378 (M + H)⁺.

d) Methyl (±)-8-methoxy-3-oxo-2-(2,2,2-trifluoroethyl)-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetate

A mixture of methyl (±)-3-carbomethoxy-4-[2-(2,2,2-trifluoroethylamino)methyl-4-methoxyphenyl]butanoate (16.71 mmole), tripropylamine (9.5 mL, 50.13 mmole), and
5 xylenes (170 mL) was heated at reflux. After 63 hr the reaction was concentrated, and the residue was chromatographed on silica (2:1 EtOAc/hexanes, load with CH₂Cl₂). The title compound (5.33 g, 92% for two steps) was obtained as a light yellow solid: TLC (40%
EtOAc/hexanes) R_f 0.49; ¹H NMR (250, CDCl₃) δ 7.04 (d, J = 8.5 Hz, 1 H), 6.80 (dd, J = 8.5, 2.6 Hz, 1 H), 6.61 (d, J = 2.6 Hz, 1 H), 5.35 (d, J = 16.8 Hz, 1 H), 3.60 - 4.30 (m, 4 H),
10 3.79 (s, 3 H), 3.71 (s, 3 H), 2.81 - 3.15 (m, 3 H), 2.46 (dd, J = 16.9, 5.5 Hz, 1 H); MS (ES) m/e 368 (M + Na)⁺, 346 (M + H)⁺.

e) Methyl (±)-8-hydroxy-2-methyl-3-oxo-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetate

A solution of BBr₃ in CH₂Cl₂ (1.0 M, 60 mL, 60 mmole) was added dropwise over
15 30 min to a solution of methyl (±)-8-methoxy-3-oxo-2-(2,2,2-trifluoroethyl)-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetate (5.16 g, 14.94 mmole) in anhydrous CH₂Cl₂ (60 mL) at -5 to -10 °C under argon. After an additional 1 hr at -5 to -10 °C, the reaction was recooled thoroughly to -10 °C and quenched by careful dropwise addition of MeOH (60 mL). The reaction was stirred at -10 to 0 °C for 1 hr, then was concentrated on the rotavap.
20 The residue was reconcentrated from MeOH (2x) then from EtOAc, then was filtered through a pad of silica gel (EtOAc eluent). Concentration of the filtrate left a yellow solid which was triturated with hot hexanes. The title compound (4.74 g, 96%) was obtained as an off-white solid: TLC (1:1 EtOAc/hexanes) R_f 0.40; ¹H NMR (400, DMSO-d₆) δ 9.28 (s, 1 H), 6.90 (d, J = 8.3 Hz, 1 H), 6.62 (dd, J = 8.3, 2.5 Hz, 1 H), 6.57 (d, J = 2.5 Hz, 1 H),
25 5.27 (d, J = 16.7 Hz, 1 H), 4.22 - 4.38 (m, 1 H), 4.07 - 4.22 (m, 1 H), 4.07 (d, J = 16.7 Hz, 1 H), 3.72 - 3.83 (m, 1 H), 3.58 (s, 3 H), 2.94 (dd, J = 17.0, 3.8 Hz, 1 H), 2.72 (dd, J = 16.7, 9.1 Hz, 1 H), 2.65 (dd, J = 17.0, 14 Hz, 1 H), 2.49 (dd, J = 16.7, 5.0 Hz, 1 H, partially obscured by residual solvent signal); MS (ES) m/e 354 (M + Na)⁺.

Preparation 7

HPLC separation of the enantiomers of methyl (±)-8-hydroxy-3-oxo-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetate

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a) Methyl (R)-(+)-8-hydroxy-3-oxo-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetate and methyl (S)-(-)-8-hydroxy-3-oxo-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetate

Methyl (±)-8-hydroxy-3-oxo-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetate was resolved into its enantiomers by chiral HPLC using the following conditions: Diacel

10 Chiralpak AS[®] column (21.2 x 250 mm), EtOH mobile phase, 7 mL/min flowrate, uv detection at 254 nm, 70 mg injection; t_R for methyl (R)-(+)-8-hydroxy-3-oxo-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetate = 21.5 min; t_R for methyl (S)-(-)-8-hydroxy-3-oxo-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetate = 39.1 min.

15

Preparation 8

HPLC separation of the enantiomers of methyl (±)-8-methoxy-3-oxo-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetate

20 a) Methyl (R)-(+)-8-methoxy-3-oxo-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetate and methyl (S)-(-)-8-methoxy-3-oxo-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetate

Methyl (±)-8-methoxy-3-oxo-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetate was resolved into its enantiomers by chiral HPLC using the following conditions: Diacel

25 Chiralpak AS[®] column (21.2 x 250 mm), CH₃CN mobile phase, 15 mL/min flowrate, uv detection at 254 nm, 500 mg injection; t_R for methyl (R)-(+)-8-methoxy-3-oxo-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetate = 10.2 min; t_R for methyl (S)-(-)-8-methoxy-3-oxo-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetate = 19.0 min.

Preparation 9

30

Demethylation of methyl (S)-(-)-8-methoxy-3-oxo-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetate

a) Methyl (S)-(-)-8-hydroxy-3-oxo-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetate

35

A solution of methyl (S)-(-)-8-methoxy-3-oxo-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetate (15.0 g, 0.057 mole) in CHCl₃ (160 mL) was added dropwise over 30 min to a solution of boron tribromide (20.53 mL, 0.217 mole) in CHCl₃ (160 mL) at -8

- °C under argon, maintaining the temperature between -5 °C and 0 °C. The reaction mixture was stirred at ca. -8 °C for 30 min and then MeOH (200 mL) was added, dropwise initially, maintaining the temperature at ca. 0 °C. The reaction mixture was concentrated to give a viscous oil which was reconcentrated from MeOH (100 mL). The oil was dissolved in
- 5 H₂O/MeOH and a small amount of dark solid was removed by filtration. The filtrate was neutralized (to pH 7) with 50 % sodium hydroxide, depositing a white solid. The suspension pH was adjusted to 4.5 by the addition of a small amount of acetic acid and the solid was collected and dried in vacuum to give afford the title compound (9.7 g, 68 %). The product was assayed for chiral purity by HPLC: Chiralpak AS[®] column (4.6 x 50
- 10 mm), 100% EtOH mobile phase, 0.5 mL/min flow rate, uv detection at 215 nm; t_R = 7.5 min (S-enantiomer, 99 %); t_R = 4.4 min (R-enantiomer, 1%).

Preparation 10

15 Preparation of 2-[(3-hydroxy-1-propyl)amino]-4,6-dimethylpyridine-N-oxide

a) 2-[(3-hydroxy-1-propyl)amino]-4,6-dimethylpyridine-N-oxide

- According to the procedure of Preparation 4, except substituting 2-chloro-4,6-dimethylpyridine-N-oxide (see Brown, E. V. *J. Amer. Chem. Soc.* **1957**, 79, 3565) for the 2-
- 20 chloropyridine-N-oxide hydrochloride, the title compound was prepared as a clear oil. MS (ES) m/e 197.2 (M + H)⁺.

Preparation 11

25 Preparation of 6-(methylamino)-2-pyridylethanol

a) 2-(*tert*-Butoxycarbonylamino)-6-picoline

- To a stirred solution of 2-amino-6-picoline (4.33 g, 40 mmol), Et₃N (6.2 mL, 40 mmol) and CH₂Cl₂ (50 mL) at 0°C was added di-*tert*-butyl dicarbonate (9.6 g, 44 mmol). After stirring at RT
- 30 overnight, the reaction mixture was concentrated in vacuum, diluted with H₂O and extracted with CH₂Cl₂ (2 x 50 mL). Drying (MgSO₄) and concentration gave the title compound as a colorless oil. MS (ES) m/e 209 (M + H)⁺.

b) 2-[(*tert*-Butoxycarbonyl)methylamino]-6-picoline

- 35 To the suspension of NaH (60% dispersion in mineral oil, 0.44 g, 11 mmol) in DMF (20 mL) at 0°C was added a solution of 2-(*tert*-butoxycarbonylamino)-6-picoline (2.1 g, 10 mmol) in DMF (30 mL). The reaction was stirred at 0°C for 15 min; then methyl iodide (1.6 g, 11 mmol) was

added. The reaction mixture was concentrated in vacuum, diluted with H₂O, and extracted with CH₂Cl₂ (3 x 50 mL). Drying (MgSO₄) and concentration gave the title compound as a colorless oil: MS (ES) m/e 223 (M + H)⁺.

5 c) Ethyl-6-[(*tert*-butoxycarbonyl)methylamino]-2-pyridylacetate

LDA (18 mmol) was prepared in THF (30 mL), cooled to -78°C, and 2-[(*tert*-butoxycarbonyl)methylamino]-6-picoline (2 g, 9 mmol) was added, forming a deep red solution. After 15 min, diethylcarbonate (18 mL, 15 mmol) was added. The burgundy-colored solution was stirred at -78°C for an additional 15 min, then the reaction was quenched with saturated NH₄Cl solution. The mixture was warmed to RT and extracted with EtOAc (3 x 30 mL). The combined organic layers were washed with brine, dried (MgSO₄), filtered and concentrated. Silica gel chromatography gave the title compound as a colorless oil: MS (ES) m/e 294 (M + H)⁺.

d) Ethyl-6-(methylamino)-2-pyridylacetate

15 A solution of ethyl-6-[(*tert*-butoxycarbonyl)methylamino]-2-pyridylacetate (0.6 g, 2 mmol) and 4 M HCl/dioxane (5 mL, 20 mmol) was stirred at RT overnight, then was concentrated. Reconcentration from toluene gave the title compound as white solid: MS (ES) m/e 195 (M + H)⁺.

e) 6-(Methylamino)-2-pyridylethanol

20 To a mechanically stirred solution of LiAlH₄ in THF (1.0 M, 20 mL, 20.4 mmol) was added dropwise a solution of ethyl-2-(methylamino)-6-pyridylacetate (0.38 g, 2 mmol) in THF (10 mL). After the addition was completed, the reaction mixture was warmed to 0°C and quenched with 10% NaOH solution. The solids were removed by filtration, and the filtrate was concentrated in vacuum. The residue was dissolved in CH₂Cl₂ and the solution was dried (MgSO₄) and concentrated. 25 Reconcentration from toluene (3 x) gave the title compound as a colorless oil: MS (ES) m/e 153 (M + H)⁺.

Preparation 12

30 Preparation of 3-[(*tert*-butoxycarbonyl)amino]-1-propanol

a) 3-[(*tert*-Butoxycarbonyl)amino]-1-propanol

A solution of di-*tert*-butyl dicarbonate (10.91 g, 50 mmole) in CH₂Cl₂ (50 mL) was added dropwise to a solution of 3-amino-1-propanol (11.5 mL, 150 mL) in CH₂Cl₂ (250 mL) at 0°C. The cloudy solution was warmed to RT and stirred for 1 hr, then was concentrated on the rotavap. The residue was taken up in H₂O (100 mL) and extracted with Et₂O (3 x 100 mL). Drying (MgSO₄) and concentration left the title compound as a

colorless oil: ^1H NMR (250 MHz, CDCl_3) δ 4.80 (br s, 1 H), 3.50 - 3.80 (m, 2 H), 3.13 - 3.42 (m, 2 H), 3.03 (br t, 1 H), 1.55 - 1.80 (m, 2 H), 1.45 (s, 9 H); MS (ES) m/e 198 ($\text{M} + \text{Na}$) $^+$.

5

Preparation 13

Preparation of 3-(4-nitrobenzyloxycarbonylamino)-1-propanol

a) 3-(4-Nitrobenzyloxycarbonylamino)-1-propanol

10 To a solution stirred under argon at room temperature of 3-amino-1-propanol (0.77 g, 1.1 mmol) and triethylamine (2.85 mL, 7 mmol) in THF (5 mL) was added a suspension of 4-nitrobenzyl chloroformate (2 g, 1 mmol) in THF (20 mL). The resulting mixture was allowed to stir at room temperature over the weekend, then was concentrated. The residue was purified by chromatography on silica gel (0%-2% MeOH/ CH_2Cl_2) to give the title
15 compound (0.80 g, 34%) as a pale yellow oil: MS (ES) m/e 254.3 ($\text{M} + \text{H}$) $^+$.

Preparation 14

Preparation of 2-[N-(3-hydroxy-1-propyl)-N-(*tert*-butoxycarbonyl)amino]pyridine-N-oxide

20

a) 2-[N-(3-hydroxy-1-propyl)-N-(*tert*-butoxycarbonyl)amino]pyridine-N-oxide

A solution of 2-[(3-hydroxy-1-propyl)amino]pyridine-N-oxide (8.0 g, 47.6 mmol) in *tert*-BuOH (80 mL) was treated with di-*tert*-butyl dicarbonate (11.4 g, 55.3 mmol). After 18h, the solution was concentrated and the residue was triturated with hexane. The
25 resulting solid was dried in vacuo to give the title compound (12.5 g, 98%) as an off-white solid: MS (ES) m/e 269.3 ($\text{M} + \text{H}$) $^+$.

Preparation 15

30

Preparation of methyl (\pm)-8-[3-[N-(1-oxopyridin-2-yl)-N-(*tert*-butoxycarbonyl)amino]-1-propyloxy]-3-oxo-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetate

a) Methyl (\pm)-8-[3-[N-(1-oxopyridin-2-yl)-N-(*tert*-butoxycarbonyl)amino]-1-propyloxy]-3-oxo-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetic acid

35

According to the procedure of Example 1(a), except substituting 2-[N-(3-hydroxy-1-propyl)-N-(*tert*-butoxycarbonyl)amino]pyridine-N-oxide for the 2-[(3-hydroxy-1-

propyl)amino]pyridine-N-oxide, the title compound was prepared as a light orange foam:
MS (ES) m/e 500.4 (M + H)⁺.

Preparation 16

5

Preparation of 2-[(3-hydroxy-1-propyl)amino]-4-methylpyridine-N-oxide

A mixture of 2-chloro-4-methylpyridine-N-oxide (12.1 g, 0.068 mole) (Brown, E. V. *J. Amer. Chem. Soc.* **1957**, *79*, 3565), 3-amino-1-propanol (10.33 mL, 0.14 mole),
10 NaHCO₃ (28 g, 0.34 mole), and *tert*-amyl alcohol (70 mL) was heated to reflux. After 16 hr, the reaction was cooled, diluted with CH₂Cl₂ (300 mL), and suction filtered to remove insoluble materials. The filtrate was concentrated and reconstituted from toluene to leave a yellow oil. Recrystallization from CH₂Cl₂/Et₂O gave the title compound (10.87 g, 88%) as a yellow solid: TLC (15% MeOH/CH₂Cl₂) R_f 0.44; ¹H NMR (400, CDCl₃) δ 7.92 (d, J = 6.7, 1 H), 7.28 (br t, 1 H), 6.43 (s, 1 H), 6.33 (dd, J = 6.6, 2.1 Hz, 1 H), 3.73 (t, J = 5.7 Hz,
15 = 6.7, 1 H), 7.28 (br t, 1 H), 6.43 (s, 1 H), 6.33 (dd, J = 6.6, 2.1 Hz, 1 H), 3.73 (t, J = 5.7 Hz, 2 H), 3.47 (q, H = 6.3 Hz, 2 H), 2.29 (s, 3 H), 1.82 - 1.88 (m, 2 H); MS (ES) m/e 183 (M + H)⁺.

Preparation 17

20

Preparation of methyl (S)-8-hydroxy-3-oxo-2-[4-(trifluoromethyl)benzyl]-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetate via alkylation of methyl (S)-8-hydroxy-3-oxo-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetate

25 a) Methyl (S)-3-oxo-8-[4-(trifluoromethyl)benzyloxy]-2-[4-(trifluoromethyl)benzyl]-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetate

To a solution of methyl (S)-8-hydroxy-3-oxo-2,3,4,5-tetrahydro-2-1H-benzazepine-4-acetate (0.31 g, 1.24 mmol) and 4-(trifluoromethyl)benzyl bromide (0.89 g, 3.72 mmol) in DMF (10 mL) was added NaH (60% suspension in oil, 0.11 g, 2.75 mmol). After stirring
30 at RT for 4h, the bulk of the DMF was removed under vacuum. The residue was partitioned between sat. NaHCO₃ and EtOAc. The aqueous phase was extracted with EtOAc and the combined organic extracts were washed with sat. NaCl, dried over Na₂SO₄ and concentrated to give a clear oil (0.90 g). Radial chromatography (5% acetone/CH₂Cl₂, silica gel, 6 m plate) gave the title compound (0.53 g) as a white foam. MS (ES) m/e 566.1
35 (M + H)⁺.

b) Methyl (S)-8-hydroxy-3-oxo-2-[4-(trifluoromethyl)benzyl]-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetate

A Parr hydrogenation flask was charged with methyl (S)-3-oxo-8-[4-(trifluoromethyl)benzyloxy]-2-[4-(trifluoromethyl)benzyl]-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetate (0.78 g, 1.38 mmol) and Pearlman's catalyst (20 mg) in MeOH (20 mL). After hydrogenating at 50 psi for 24 h, the reaction vessel was vented and the catalyst was removed by filtration. Removal of solvent gave a white foam (0.60 g). Radial chromatography (5% acetone/CH₂Cl₂, silica gel, 6 m plate) gave the title compound (0.42 g) as a white foam. ¹H NMR (250 MHz, CDCl₃) δ 7.50 (d, J = 8.5 Hz, 2H), 7.23 (d, J = 8.5 Hz, 2H), 6.90 (d, J = 7.5 Hz, 1H), 6.67 (dd, J = 7.5, 3.4 Hz, 1H), 6.39 (d, J = 3.4 Hz, 1H), 5.05 (m, 2 H), 4.35 (d, J = 15.4 Hz, 1H), 3.85 (m, 1H), 3.70 (s, 3H), 3.60 (m, 1H), 2.95 (m, 4H), 2.45 (dd, J = 17.1, 5.1 Hz, 1H).

Preparation 18

Preparation of methyl (S)-8-hydroxy-3-oxo-2-[4-(trifluoromethyl)benzyl]-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetate via enantioselective synthesis

a) 4-Bromo-3-bromomethylanisole

To a stirred solution of 4-bromo-3-methylanisole (100 g, 497 mmol) in dry dichloromethane (500 mL) was added N-bromosuccinimide (97 g, 545 mmol) followed by benzoyl peroxide (6 g, 25 mmol). The reaction was gently refluxed with a 150 watt flood lamp with reflector placed approximately 12 inches from the reaction flask. After 24 h the reaction was concentrated by rotary evaporation to half its volume and allowed to sit for 4 h. The white precipitate which formed was filtered off and rinsed with a small volume of dichloromethane. The filtrate was concentrated to dryness and the remaining solid was triturated with hexanes and filtered. Drying under vacuum gave the title compound (100.25 g, 72%) as white needles: GC t_R = 6.56 min (HP 530 μm x 20 m methylsilicone column, He carrier flow 20 mL/min, 100 °C initial temp., 1 min initial time, 10 °C/min rate, 200 °C final temp., 1 min final time); ¹H NMR (400 MHz, CDCl₃) δ 7.44 (d, J = 10 Hz, 1 H), 6.99 (d, J = 3 Hz, 1 H), 6.73 (dd, 1H), 4.55 (s, 2H), 3.80 (s, 3H).

b) 3-[N-(4-Trifluoromethylbenzyl)aminomethyl]-4-bromoanisole

To a stirred solution of 4-bromo-3-bromomethylanisole (35 g, 125 mmol) in anhydrous DMSO (50 mL) and dry THF (50 mL) was added 4-trifluoromethylbenzylamine (30 g, 171 mmol) followed by triethylamine (18 mL, 129 mmol). After stirring for 18 h at RT the reaction was concentrated, diluted with aqueous 1 N NaOH (250 mL) and extracted

with Et₂O (2 x 250 mL). The combined organic layers were washed with brine, dried (Na₂SO₄), and concentrated to dryness. The residue which remained was purified by flash chromatography on silica gel (10 to 20% EtOAc/CHCl₃) to give the title compound (34.17 g, 73%): TLC (20% EtOAc/CHCl₃) R_f 0.63; ¹H NMR (400 MHz, CDCl₃) δ 7.59 (d, J = 8.2 Hz, 2H), 7.49 (d, J = 8.2 Hz, 2H), 7.43 (d, J = 8.6 Hz, 1H), 6.96 (d, J = 3.1 Hz, 1H), 6.70 (dd, 1H), 3.86 (s, 2H), 3.84 (s, 2H), 3.79 (s, 3H), 1.75 (br s, 1H).

c) 3-[N-(tert-Butoxycarbonyl)-N-(4-trifluoromethylbenzyl)aminomethyl]-4-bromoanisole

To a stirred solution of 3-[N-(4-trifluoromethylbenzyl)aminomethyl]-4-bromoanisole (34.17 g, 91 mmol) in dry THF (100 mL) was added di-tert-butyl dicarbonate (22 g, 101 mmol). The reaction was stirred under argon for 18 h (vigorous gas evolution was observed). Concentration and silica gel chromatography (5 to 10% EtOAc/hexane) gave the title compound (41.09 g, 95%) as a clear oil: TLC (silica, 20% EtOAc/hexane) R_f 0.44; ¹H NMR (400 MHz, CDCl₃) δ 7.57 (d, J = 8.3 Hz, 2H), 7.40 (d, J = 8.3 Hz, 2H), 7.39-7.33 (m, 2H), 6.83 and 6.72 (2 s, 1H), 6.71 (dd, 1H), 4.54 and 4.50 (2 s, 2H), 4.43 (s, 2H), 3.75 (s, 3H), 1.47 (s, 9H).

d) Methyl 2-[N-(tert-butoxycarbonyl)-N-(4-trifluoromethylbenzyl)aminomethyl]-4-methoxycinnamate

A solution of 3-[N-(tert-butoxycarbonyl)-N-(4-trifluoromethylbenzyl)aminomethyl]-4-bromoanisole (37.08 g, 78 mmol), methyl acrylate (35 mL, 390 mmol), palladium acetate (0.88g, 3.9 mmol), tri-*o*-tolylphosphine (2.38 g, 7.8 mmol), and diisopropylethylamine (31 mL, 178 mmol) in acetonitrile (200 mL) was deoxygenated (3 evacuation/argon purge cycles), then was heated to reflux under argon (oil bath set at 80 °C). After 6 hr additional palladium acetate (0.88 g, 3.9 mmol) and tri-*o*-tolylphosphine ((2.38 g, 7.8 mmol) were added and the reaction was stirred under reflux for an additional 18 h. The reaction was concentrated to dryness, and the residue was taken up in 1:1 Et₂O/petroleum ether (300 mL) and allowed to stand for 4 h. A gray-colored precipitate was filtered off and washed with a small volume of 1:1 Et₂O/petroleum ether (100 mL). The orangish-red filtrate was concentrated and purified by flash chromatography on silica gel (15% ethyl acetate/hexanes). The resulting residue was taken up in hexane, and the mixture was allowed to stand for several hr, then was filtered to remove a yellow precipitate. Concentration of the filtrate left the title compound (34.52 g, 92%) as a thick yellow oil: TLC (silica, 20% EtOAc/hexanes) R_f 0.45; ¹H NMR (400 MHz, CDCl₃) δ 7.80 (br s, 1H), 7.57 (d, J = 8.1 Hz, 2H), 7.53 (d, J = 8.6 Hz, 1H), 7.29 (br s, 2H), 6.83 (dd, 1H), 6.72 (br s, 1H), 6.23 (d, J = 15.7 Hz, 1H), 4.58 and 4.53 (2 br s, 2H), 4.46 and 4.37 (2 br s, 2H), 3.80 (s, 3H), 3.77 (s, 3H), 1.49 (s, 9H).

e) Methyl 2-[N-(tert-butoxycarbonyl)-N-(4-trifluoromethylbenzyl)aminomethyl]-4-methoxydihydrocinnamate

To 10% Pd/C (5 g, 4.7 mmol, prewetted with DMF) was added a solution of methyl 2-[N-(tert-butoxycarbonyl)-N-(4-trifluoromethylbenzyl)aminomethyl]-4-methoxycinnamate (34.52 g, 72 mmol) in methanol (100 mL). The mixture was shaken under hydrogen (50 psi) in a Parr apparatus for 7 hr, then was filtered through a pad of celite® to remove the catalyst. The filtrate was concentrated to afford the title compound (34.15 g, 98%) as a colorless oil: ¹H NMR (400 MHz, CDCl₃) δ 7.58 (d, J = 8.1 Hz, 2H), 7.31 (br s, 2H), 7.09 (d, J = 8.4 Hz, 1H), 6.76 (dd, 1H), 6.66 (s, 1H), 4.47 (br s, 2H), 4.40 (br s, 2H), 3.76 (s, 3H), 3.63 (s, 3H), 2.79 (br s, 2H), 2.47 (t, 2H), 1.48 (s, 9H).

f) 2-[N-(tert-Butoxycarbonyl)-N-(4-trifluoromethylbenzyl)aminomethyl]-4-methoxydihydrocinnamic acid

To a stirred solution of 2-[N-(tert-butoxycarbonyl)-N-(4-trifluorobenzyl)aminomethyl]-4-methoxydihydrocinnamic acid (34.15 g, 71 mmol) in dioxane (150 mL) was added aqueous 1 N NaOH (85 mL, 85 mmol). The cloudy reaction was stirred at RT for 4 h. The resulting homogeneous solution was neutralized with aqueous 1 N HCl (85 mL, 85 mmol) and extracted with ethyl acetate (2 x 250 mL). The combined organic layers were washed with brine (250 mL), dried (MgSO₄) and concentrated to give the title compound (34.60 g, 100%) as a thick clear oil: TLC (95:4:1 CHCl₃/MeOH/HOAc) R_f 0.49; ¹H NMR (400 MHz, CDCl₃) δ 7.58 (d, J = 8.1 Hz, 2H), 7.30 (br s, 2H), 7.09 (d, J = 8.4 Hz, 1H), 6.78 (dd, 1H), 6.65 (d, J = 2.6 Hz, 1H), 4.47 (br s, 2H), 4.42 (br s, 2H), 3.76 (s, 3H), 2.81 (br s, 2H), 2.53 (t, 2H), 1.47 (s, 9H).

g) (R)-4-Benzyl-2-oxazolidinonyl 2-[N-(tert-butoxycarbonyl)-N-(4-trifluoromethylbenzyl)aminomethyl]-4-methoxydihydrocinnamide

To a stirred solution of 2-[N-(tert-butoxycarbonyl)-N-(4-trifluoromethylbenzyl)aminomethyl]-4-methoxydihydrocinnamic acid (34.60 g, 71 mmol) and pyridine (6.9 mL, 85 mmol) in dry dichloromethane (200 mL) under Argon was added cyanuric fluoride (4.4 mL, 48 mmol) via syringe. The reaction was stirred for 4 h at RT. The resulting thick suspension was filtered through a pad of celite® and rinsed with a small volume of dry dichloromethane (50 mL). The clear filtrate was poured into a separatory funnel and washed with ice-cold water (500 mL). Drying (MgSO₄) and concentration left the crude acid fluoride (34.70 g, 100%) which was used without further purification.

To a stirred solution of (R)-4-benzyl-2-oxazolidinone (13.8 g, 78 mmol) in dry THF (300 mL) under argon at -78 °C was added via syringe a solution of n-BuLi in hexanes

(2.5 M, 30 mL, 75 mmol). The reaction was stirred at -78 °C for 15 min, then a solution of the above acid fluoride (34.70 g, 71 mmol) in dry THF (100 mL) was added via syringe. The reaction was stirred for 1 h at -78 °C then was quenched with saturated NH₄Cl and extracted with ethyl acetate (2 x 200 mL). The combined organic layers were washed with
5 brine (400 mL), dried (MgSO₄), and concentrated to dryness. Purification by flash chromatography on silica gel (20% ethyl acetate/hexanes) gave the title compound (40.34 g, 90%) as a thick clear oil: TLC (20% EtOAc/hexane) R_f 0.21; ¹H NMR (400 MHz, CDCl₃) δ 7.58 (d, J = 8.1 Hz, 2H), 7.33-7.26 (m, 5H), 7.16 (m, 3H), 6.77 (dd, 1H), 6.67 (d, J = 2.5 Hz, 1H), 4.62 (m, 1H), 4.60-4.40 (m, 4H), 4.16 (m, 2H), 3.76 (s, 3H), 3.27 (dd, 1H),
10 3.21-3.10 (m, 2H), 2.88 (br s, 2H), 2.72 (dd, 1H), 1.48 (s, 9H).

h) (R)-4-Benzyl-2-oxazolidinonyl 3-[2-[N-(tert-butoxycarbonyl)-N-(4-trifluoromethylbenzyl)aminomethyl]-4-methoxyphenyl]-2(S)-methoxycarbonylmethyl-propionamide

15 To a stirred solution of (R)-4-benzyl-2-oxazolidinonyl 2-[N-(tert-butoxycarbonyl)-N-(4-trifluoromethylbenzyl)aminomethyl]-4-methoxydihydrocinnamide (40.30 g, 64 mmol) in dry THF (300 mL) at -78 °C was added a solution of lithium bis(trimethylsilyl)amide (70 mL, 1 M in THF, 70 mmol) via syringe. After 30 min, methyl bromoacetate (30 mL, 317 mmol) was added via syringe. After another 30 min at -78 °C the reaction was allowed to
20 warm to -20 °C and stirred for an additional 6 h. The reaction was quenched with saturated NH₄Cl (400 mL) and extracted with ethyl acetate (2 x 200 mL). The combined organic layers were washed with brine (300 mL), dried (MgSO₄), and concentrated to dryness. Purification by flash chromatography on silica gel (20% ethyl acetate/hexanes) gave the title compound (38.62 g, 86%) as a white solid: HPLC (Altex Ultrasphere™-Si 5u, 20%
25 EtOAc/hexane) showed approximately 20% unalkylated starting material was still present. HPLC of the crude reaction mixture gave a de of 90% for the reaction; ¹H NMR (400 MHz, CDCl₃) δ 7.57 (d, J = 8.1 Hz, 2H), 7.40-7.11 (m, 8H), 6.71 (dd, 1H), 6.63 (d, J = 2.7 Hz, 1H), 4.57-4.34 (m, 6H), 4.03 (d, J = 8.6 Hz, 1H), 3.85 (t, 1H), 3.72 (s, 3H), 3.61 (s, 3H), 3.28 (dd, 1H), 2.90 (dd, 1H), 2.86-2.71 (m, 2H), 2.70 (dd, 1H), 2.44 (m, 1H), 1.48 and 1.46
30 (2s, 9H).

i) Methyl (S)-8-methoxy-3-oxo-2-(4-trifluoromethylbenzyl)-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetate

To a stirred solution of (R)-4-benzyl-2-oxazolidinonyl 3-[2-[N-(tert-butoxycarbonyl)-N-(4-trifluoromethylbenzyl)aminomethyl]-4-methoxyphenyl]-2(S)-methoxycarbonylmethyl-propionamide (38.0 g, 54 mmol) in THF (300 mL) and water (100 mL) was added dropwise at 0 °C over 30 min a solution of 30% H₂O₂ (18.9 mL) and LiOH

· H₂O (2.3 g, 55 mmol) in water (62 mL). The cloudy solution was stirred for an additional 1 h at 0 °C. The resulting homogeneous solution was treated slowly with a solution of sodium sulfite (34.3 g, 272 mmol) in water (175 mL) at 0 °C, then was acidified with an ice-cold solution of concentrated HCl (35 mL) in water (150 mL). The reaction was
 5 extracted with ethyl acetate (2x200 mL), and the combined organic layers were washed with brine (400 mL), dried (MgSO₄) and concentrated to dryness. The resulting residue was treated with 4.0 M HCl in dioxane (400 mL) with stirring at RT (slow gas evolution was observed). After 1 h, the reaction was concentrated and reconcentrated from 1:1 CHCl₃/toluene (2 x), then the residue (37.65 g) was taken up in dry DMF (400 mL). To
 10 this solution with stirring under argon at 0 °C in a Dewar flask were added triethylamine (15.3 mL, 109 mmol) and NaHCO₃ (22.9 g, 273 mmol), followed by diphenylphosphoryl azide (13 mL, 60 mmol). After stirring for 24 h at 0 °C the reaction was concentrated to dryness. The residue was taken up in ethyl acetate (400 mL), and washed sequentially with water (300 mL) and brine (300 mL). Drying (MgSO₄), concentration, and flash
 15 chromatography on silica gel (35% ethyl acetate/hexanes) gave the title compound (16.87 g, 74%) as a clear thick oil: TLC (40% EtOAc/hexane) R_f 0.50; MS (ES) m/e 422.3 (M + H)⁺; ¹H NMR (400 MHz, CDCl₃) δ 7.52 (d, J = 8.1, 2H), 7.29 (d, J = 8.1 Hz, 2H), 7.02 (d, J = 8.5 Hz, 1H), 7.75 (dd, 1H), 6.36 (d, J = 2.7 Hz, 1H), 5.18 (d, J = 16.5 Hz, 1H), 4.96 (d, J = 15.4 Hz, 1H), 4.48 (d, J = 15.4 Hz, 1H), 3.87 (m, 1H), 3.74 (d, J = 16.5 Hz, 1H), 3.73 (s,
 20 3H), 3.71 (s, 3H), 3.08 (dd, 1H), 3.02 (dd, 1H), 2.95 (dd, 1H), 2.48 (dd, 1H).

j) Methyl (S)-8-hydroxy-3-oxo-2-(4-trifluoromethylbenzyl)-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetate

A solution of boron tribromide in CH₂Cl₂ (1.0 M, 160 mL, 160 mmol) was added
 25 dropwise over 30 min to a solution of methyl (S)-8-methoxy-3-oxo-2-(4-trifluoromethylbenzyl)-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetate (16.67 g, 39.6 mmol) in anhydrous CH₂Cl₂ (150 mL) at -20 °C under argon. After an additional 1.5 hr at -15 to -20 °C, the reaction was recooled to -20 °C and quenched by careful dropwise addition of MeOH (160 mL). The reaction was stirred at -10 to 0 °C for 1 hr, then was
 30 concentrated on the rotavap. The residue was reconcentrated from MeOH (2 x). Purification by flash chromatography on silica gel (50 to 100% ethyl acetate/hexanes) gave the title compound (14.87 g, 92%) as a white solid: [α]_D -81.8° (c, 1.0, MeOH); TLC (silica, 50% EtOAc/hexane) R_f 0.54; MS (ES) m/e 408.2 (M + H)⁺; ¹H NMR (400, CDCl₃ + 2% DMSO-d₆) δ 7.53 (d, J = 8.1 Hz, 2H), 7.31 (d, J = 8.1 Hz, 2H), 6.93 (d, J = 8.4 Hz, 1H), 6.70 (dd, 1H), 6.41 (d, J = 2.3 Hz, 1H), 5.16 (d, J = 16.4 Hz, 1H), 5.01 (d, J = 15.6 Hz, 1H), 4.39 (d, J = 15.6 Hz, 1H), 3.84 (m, 1H), 3.73 (d, J = 16.4 Hz, 1H), 3.71 (s, 3H), 3.01 (dd, 1H), 2.98 (m, 1H), 2.90 (dd, 1H), 2.47 (dd, 1H).

Preparation 19

5 HPLC separation of the enantiomers of methyl (±)-8-methoxy-3-oxo-2-(2,2,2-trifluoroethyl)-2,3,4,5-tetrahydro-2-benzazepine-4-acetate

a) Methyl (R)-(+)-8-methoxy-3-oxo-2-(2,2,2-trifluoroethyl)-2,3,4,5-tetrahydro-2-benzazepine-4-acetate and methyl (S)-(-)-8-methoxy-3-oxo-2-(2,2,2-trifluoroethyl)-2,3,4,5-tetrahydro-2-benzazepine-4-acetate

10 Methyl (±)-8-methoxy-3-oxo-2-(2,2,2-trifluoroethyl)-2,3,4,5-tetrahydro-2-benzazepine-4-acetate was resolved into its enantiomers by chiral HPLC using the following conditions: Diacel Chiralcel OJ® column (21.2 x 250 mm), methanol mobile phase, 15 mL/min flowrate, uv detection at 295 nm, 400 mg injection; t_R for methyl (R)-(+)-8-methoxy-3-oxo-2-(2,2,2-trifluoroethyl)-2,3,4,5-tetrahydro-2-benzazepine-4-acetate =
15 4.9 min; t_R for methyl (S)-(-)-8-methoxy-3-oxo-2-(2,2,2-trifluoroethyl)-2,3,4,5-tetrahydro-2-benzazepine-4-acetate = 6.6 min.

Preparation 20

20 HPLC separation of the enantiomers of methyl (±)-8-hydroxy-3-oxo-2-(2,2,2-trifluoroethyl)-2,3,4,5-tetrahydro-2-benzazepine-4-acetate

a) Methyl (R)-(+)-8-hydroxy-3-oxo-2-(2,2,2-trifluoroethyl)-2,3,4,5-tetrahydro-2-benzazepine-4-acetate and methyl (S)-(-)-8-hydroxy-3-oxo-2-(2,2,2-trifluoroethyl)-2,3,4,5-tetrahydro-2-benzazepine-4-acetate

25 Methyl (±)-8-hydroxy-3-oxo-2-(2,2,2-trifluoroethyl)-2,3,4,5-tetrahydro-2-benzazepine-4-acetate was resolved into its enantiomers by chiral HPLC using the following conditions: Diacel Chiralcel OD® column (21.2 x 250 mm), 20% ethanol in hexane mobile phase, 10 mL/min, uv detection at 254 nm, 100 mg injection; t_R for methyl
30 (R)-(+)-8-hydroxy-3-oxo-2-(2,2,2-trifluoroethyl)-2,3,4,5-tetrahydro-2-benzazepine-4-acetate = 14.4 min; t_R for methyl (S)-(-)-8-hydroxy-3-oxo-2-(2,2,2-trifluoroethyl)-2,3,4,5-tetrahydro-2-benzazepine-4-acetate = 18.5 min.

Preparation 21Preparation of methyl (S)-8-hydroxy-3-oxo-2-(2,2,2-trifluoroethyl)-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetate via enantioselective synthesis

5

a) 4-Bromo-3-bromomethylanisole

To a stirred solution of 4-bromo-3-methylanisole (100 g, 497 mmol) in dry dichloromethane (500 mL) was added N-bromosuccinimide (97 g, 545 mmol) followed by benzoyl peroxide (6 g, 25 mmol). The reaction was gently refluxed with a 150 watt flood lamp with reflector placed approximately 12 inches from the reaction flask. After 24 h the reaction was concentrated by rotary evaporation to half its volume and allowed to sit for 4 h. The white precipitate which formed was filtered off and rinsed with a small volume of dichloromethane. The filtrate was concentrated to dryness and the remaining solid was triturated with hexanes and filtered. Drying under vacuum gave the title compound (100.25 g, 72%) as white needles: GC (t_R = 6.56 min (HP 530 μ m x 20 m methylsilicone column, He carrier flow 20 mL/min, 100 °C initial temp., 1 min initial time, 10 °C/min rate, 200 °C final temp., 1 min final time); 1H NMR (400 MHz, $CDCl_3$) δ 7.44 (d, J = 10 Hz, 1 H), 6.99 (d, J = 3 Hz, 1 H), 6.73 (dd, 1H), 4.55 (s, 2H), 3.80 (s, 3H).

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20 b) 3-[N-(2,2,2-Trifluoroethyl)aminomethyl]-4-bromoanisole

2,2,2-Trifluoroethylamine (24 g, 242 mmol) was added rapidly to a stirred solution of 4-bromo-3-bromomethylanisole (33.6 g, 120 mmol) in anhydrous DMSO (125 mL) at RT. The reaction warmed to approximately 30 - 35 °C. After stirring for 18 hr, the reaction was diluted with ice-cold 1 N NaOH (200 mL) and extracted with Et_2O (2 x 300 mL). The combined organic layers were washed with brine (300 mL), dried ($MgSO_4$), and concentrated to give the title compound (41.35 g, 96%) as a pale yellow oil: TLC (toluene) R_f 0.32; 1H NMR (400 MHz, $CDCl_3$) δ 7.43 (d, J = 9 Hz, 1H), 6.97 (d, J = 3 Hz, 1H), 6.71 (dd, 1H), 3.93 (br s, 2H), 3.80 (s, 3H), 3.18 (m, 2H), 1.86 (br s, 1H).

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30 c) 3-[N-(tert-Butoxycarbonyl)-N-(2,2,2-trifluoroethyl)aminomethyl]-4-bromoanisole

To 3-[N-(2,2,2-trifluoroethyl)aminomethyl]-4-bromoanisole (41.35 g, 137 mmol) was added di-tert-butyl dicarbonate (36 g, 165 mmol, liquefied by warming in a hot water bath). The reaction was rinsed down with a small amount of dichloromethane (~20 mL) and stirred under argon in a 50 °C oil bath for 18 h (slow gas evolution was observed). After concentration by rotary evaporation under vacuum the resulting residue was diluted with hexanes (100 mL) and the solution was seeded with a small amount of the pure solid product (obtained from a previous reaction by silica gel chromatography using 10%

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EtOAc/hexanes as eluent). The mixture was allowed to stand at RT for several hours then was placed in the refrigerator overnight. The product was collected by suction filtration and washed with hexanes. Drying in vacuum gave the title compound (48.54 g, 88%) as a colorless solid: TLC (10% EtOAc/toluene) R_f 0.52; ^1H NMR (400 MHz, CDCl_3) δ 7.44 (d, $J = 9$ Hz, 1H), 6.75 (dd, 1H), 6.71 (s, 1H), 4.65 and 4.58 (2s, 2H), 3.90 and 3.78 (2m, 2H), 3.77 (s, 3H), 1.51 and 1.42 (2s, 9H).

d) Methyl 2-[N-(tert-butoxycarbonyl)-N-(2,2,2-trifluoroethyl)aminomethyl]-4-methoxycinnamate

10 A solution of 3-[N-(tert-butoxycarbonyl)-N-(2,2,2-trifluoroethyl)aminomethyl]-4-bromoanisole (48.19 g, 121 mmol), methyl acrylate (55 mL, 605 mmol), palladium acetate (1.36 g, 6.1 mmol), tri-*o*-tolylphosphine (3.69 g, 12 mmol), and diisopropylethylamine (49 mL, 278 mmol) in acetonitrile (200 mL) was deoxygenated (3 x evacuation/argon purge cycles), then was heated to reflux under argon in oil bath set at 80 °C. After 6 hr additional
15 palladium acetate (1.36 g, 6.1 mmol) and tri-*o*-tolylphosphine (3.69 g, 12 mmol) were added and the reaction was stirred under reflux for an additional 18 h. The reaction was concentrated to dryness, and the residue was taken up in 1:1 Et_2O /petroleum ether (300 mL) and allowed to stand for 4 h. A gray-colored precipitate was filtered off and washed with a small volume of 1:1 Et_2O /petroleum ether (~100 mL). The orangish-red filtrate was
20 concentrated and purified by flash chromatography on silica gel (15% ethyl acetate/hexanes). The resulting residue was taken up in hexane, and the mixture was allowed to stand for 2 hr, then was filtered to remove a yellow precipitate. Concentration of the filtrate left the title compound (45.85 g, 94%) as a yellow oil: TLC (20% EtOAc/hexane) R_f 0.50; ^1H NMR (400 MHz, CDCl_3) δ 7.84 (d, $J = 16$ Hz, 1H), 7.57 (d, $J = 9$ Hz, 1H), 6.86 (dd, 1H), 6.74 and 6.72 (2s, 1H), 6.26 (d, $J = 16$ Hz, 1H), 4.74 and 4.70 (2s, 2H), 3.83 (s, 3H), 3.79 (s, 3H), 3.80 and 3.66 (2m, 2H), 1.51 and 1.45 (2s, 9H).

e) Methyl 2-[N-(tert-butoxycarbonyl)-N-(2,2,2-trifluoroethyl)aminomethyl]-4-methoxydihydrocinnamate

30 To 10% Pd/C (5 g, 4.7 mmol, prewetted with DMF) was added a solution of methyl 2-[N-(tert-butoxycarbonyl)-N-(2,2,2-trifluoroethyl)amino]methyl-4-methoxycinnamate (45.85 g, 113 mmol) in methanol (100 mL). The mixture was shaken under hydrogen (50 psi) in a Parr apparatus for 6 hr, then was filtered through a pad of celite® to remove the catalyst. The filtrate was concentrated to afford the title compound (43.71 g, 95%) as a
35 colorless oil: ^1H NMR (400 MHz, CDCl_3) δ 7.11 (d, $J = 8$ Hz, 1H), 6.78 (dd, 1H), 6.65 (s, 1H), 4.63 and 4.60 (2s, 2H), 3.84 and 3.70 (2m, 2H), 3.77 (s, 3H), 3.66 (s, 3H), 2.86 (t, 2H), 2.53 (t, 2H), 1.50 and 1.44 (2s, 9H).

f) 2-[N-(tert-Butoxycarbonyl)-N-(2,2,2-trifluoroethyl)aminomethyl]-4-methoxydihydrocinnamic acid

To a stirred solution of methyl 2-[N-(tert-butoxycarbonyl)-N-(2,2,2-trifluoroethyl)aminomethyl]-4-methoxydihydrocinnamate (43.71 g, 108 mmol) in dioxane (200 mL) was added aqueous 1 N NaOH (130 mL, 130 mmol). The cloudy reaction was stirred at RT for 4 h. The resulting a homogeneous solution was neutralized with 1 N HCl (130 mL, 130 mmol) and extracted with ethyl acetate (2 x 250 mL). The combined organic layers were washed with brine (250 mL), dried (MgSO₄), and concentrated to give the title compound (45.01 g, 100%) as a thick clear oil: TLC (95:4:1 CHCl₃, MeOH, HOAc) R_f 0.49.

g) (R)-4-Benzyl-2-oxazolidinonyl 2-[N-(tert-butoxycarbonyl)-N-(2,2,2-trifluoroethyl)aminomethyl]-4-methoxydihydrocinnamide

To a stirred solution of 2-[N-(tert-butoxycarbonyl)-N-(2,2,2-trifluoroethyl)aminomethyl]-4-methoxydihydrocinnamic acid (45.0 g, 108 mmol) and pyridine (10 mL, 124 mmol) in dry dichloromethane (400 mL) under argon was added cyanuric fluoride (6.8 mL, 74 mmol) via syringe. The reaction was stirred for 4 h at RT. The resulting thick suspension was filtered through a pad of celite®, and the filter pad was rinsed with a small volume of dry dichloromethane (50 mL). The clear filtrate was poured into a separatory funnel and washed with ice-cold water (750 mL). Drying (MgSO₄) and concentration left the crude acid fluoride (43.32 g, 100%) which was used without further purification.

To a stirred solution of (R)-4-benzyl-2-oxazolidinone (21 g, 119 mmol) in dry THF (400 mL) under argon at -78 °C was added via syringe a solution of n-BuLi in hexanes (2.5 M, 113 mmol). The reaction was stirred at -78 °C for 15 min, then a solution of the above acid fluoride (43.32 g, 108 mmol) in dry THF (100 mL) was added via syringe. The reaction was stirred for 1 h at -78°C then was quenched with saturated NH₄Cl and extracted with ethyl acetate (2 x 250 mL). The combined organic layers were washed with brine (500 mL), dried (MgSO₄), and concentrated to dryness. Purification by flash chromatography on silica gel (20% ethyl acetate/hexanes) gave the title compound (55.27 g, 91%) as a thick clear oil: TLC (silica, 20% EtOAc/hexane) R_f 0.24; ¹H NMR (400 MHz, CDCl₃) δ 7.34-7.26 (m, 3H), 7.19-7.16 (m, 3H), 6.78 (dd, 1H), 6.67 (s, 1H), 4.68-4.63 (m, 3H), 4.21-4.11 (m, 2H), 3.87 and 3.74 (2m, 2H), 3.77 (s, 3H), 3.28 (dd, 1H), 3.17 (m, 2H), 2.93 (m, 2H), 2.75 (dd, 1H), 1.50 and 1.45 (2s, 9H).

h) (R)-4-Benzyl-2-oxazolidinonyl 3-[2-[N-(tert-butoxycarbonyl)-N-(2,2,2-trifluoroethyl)aminomethyl]-4-methoxyphenyl]-2(S)-methoxycarbonylmethyl-propionamide

To a stirred solution of (R)-4-benzyl-2-oxazolidinonyl 2-[N-(tert-butoxycarbonyl)-N-(2,2,2-trifluoroethyl)aminomethyl]-4-methoxydihydrocinnamide (55.2 g, 100 mmol) in dry THF (300 mL) at -78 °C was added a solution of lithium bis(trimethylsilyl)amide (115 mL, 1 M in THF, 115 mmol) via syringe. After 30 min methyl bromoacetate (47 mL, 497 mmol) was added via syringe. After another 30 min at -78 °C the reaction was allowed to warm to -20 °C and stirred for an additional 6h. The reaction was quenched with saturated NH₄Cl (400 mL) and extracted with ethyl acetate (2 x 250 mL). The combined organic layers were washed with brine (400 mL), dried (MgSO₄), and concentrated to dryness. Purification by flash chromatography on silica gel (20% ethyl acetate/hexanes) gave the title compound (52.44 g, 75%) as a white solid: HPLC (Altex Ultrasphere™-Si 5u, 20% EtOAc/hexane) showed approximately 6-7% unalkylated starting material was still present. HPLC of the crude reaction mixture gave a de of 86% for the reaction; ¹H NMR (400 MHz, CDCl₃) δ 7.35-7.13 (m, 6H), 6.73 (dd, 1H), 6.64 (s, 1H), 4.69-4.53 (m, 4H), 4.04 (d, 1H), 3.87 (t, 1H), 3.85-3.72 (m, 2H), 3.75 (s, 3H), 3.64 (s, 3H), 3.31 (dd, 1H), 2.95 (dd, 1H), 2.92-2.71 (m, 2H), 2.71 (dd, 1H), 2.50 (m, 1H), 1.50 and 1.47 (2 br s, 9H).

i) Methyl (S)-8-methoxy-3-oxo-2-(2,2,2-trifluoroethyl)-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetate

To a stirred solution of (R)-4-benzyl-2-oxazolidinonyl 3-[2-[N-(tert-butoxycarbonyl)-N-(2,2,2-trifluoroethyl)aminomethyl]-4-methoxyphenyl]-2(S)-methoxycarbonylmethyl-propionamide (52.40 g, 75 mmol) in THF (300 mL) and water (100 mL) was added dropwise at 0 °C over 30 min a solution of 30% H₂O₂ (26 mL) and LiOH · H₂O (3.2 g, 75 mmol) in water (85 mL). The cloudy solution was stirred for an additional 1 h at 0 °C. The resulting homogeneous solution was treated slowly with a solution of sodium sulfite (46 g, 365 mmol) in water (240 mL) at 0 °C, then was acidified with an ice-cold solution of concentrated HCl (45 mL) in water (200 mL). The reaction was extracted with ethyl acetate (2 x 300 mL), and the combined organic layers were washed with brine (600 mL), dried (MgSO₄) and concentrated to dryness. The resulting residue was treated with 4.0 M HCl in dioxane (500 mL) with stirring at RT (slow gas evolution was observed). After 1 h, the reaction was concentrated and reconstituted from 1:1 CHCl₃/toluene (2 x), then the residue (48.89 g) was taken up in dry DMF (500 mL). To this solution with stirring under argon at 0 °C in a Dewar flask were added triethylamine (21 mL, 150 mmol) and NaHCO₃ (31.5 g, 375 mmol), followed by diphenylphosphoryl azide (18 mL, 83.5 mmol). After stirring for 24 h at 0 °C, the reaction was concentrated to

dryness. The residue was taken up in ethyl acetate (500 mL) and washed sequentially with water (400 mL) and brine (400 mL). Drying (MgSO₄), concentration, and flash chromatography on silica gel (30% ethyl acetate/hexanes) gave the title compound (21.81 g, 84%) as a white solid: $[\alpha]_D -132.6^\circ$ (c, 1.0, MeOH); TLC (40% EtOAc/hexane) R_f 0.56; 5 chiral HPLC (Chiracel OD, 20% EtOH/hexane) $k' = 2.05$; the opposite enantiomer from a racemic standard had $k' = 1.86$ (none detected); MS (ES) m/e 346.2 (M + H)⁺; ¹H NMR (400 MHz, CDCl₃) δ 7.03 (d, J = 8.5 Hz, 1H), 6.79 (dd, 1H), 6.61 (d, J = 2.6 Hz, 1H), 5.35 (d, J = 16.7 Hz, 1H), 4.17 (m, 1H), 4.0 (m, 1H), 3.99 (d, J = 16.7 Hz, 1H), 3.84 (m, 1H), 3.79 (s, 3H), 3.71 (s, 3H), 3.01 (m, 2H), 2.91 (dd, 1H), 2.47 (dd, 1H). Anal. Calcd for 10 C₁₆H₁₈F₃NO₄: C, 55.65; H, 5.25; N, 4.06. Found: C, 55.62; H, 5.27; N, 4.04.

j) Methyl (S)-8-hydroxy-2-methyl-3-oxo-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetate

A solution of boron tribromide in CH₂Cl₂ (1.0 M, 250 mL, 250 mmol) was added dropwise over 30 min to a solution of methyl (S)-8-methoxy-3-oxo-2-(2,2,2-trifluoroethyl)-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetate (21.5 g, 62.3 mmol) in anhydrous CH₂Cl₂ 15 (230 mL) at -20 °C under argon. After an additional 1.5 hr at -15 to -20 °C, the reaction was recooled to -20 °C and quenched by careful dropwise addition of MeOH (250 mL). The reaction was stirred at -10 to 0 °C for 1 hr, then was concentrated on the rotavap. The residue was reconcentrated from MeOH (2 x). Purification by flash chromatography on 20 silica gel (50% ethyl acetate/hexanes) gave the title compound (19.38 g, 94%) as a white solid: $[\alpha]_D -130.5^\circ$ (c 1.0, MeOH); TLC (silica, 40% EtOAc/hexane) R_f 0.40; MS (ES) m/e 332.1 (M + H)⁺; ¹H NMR (400, CDCl₃ + 2% DMSO-d₆) δ 6.92 (d, J = 8.3 Hz, 1 H), 6.71 (dd, 1H), 6.58 (d, J = 2.5 Hz, 1H), 5.29 (d, J = 16.7 Hz, 1 H), 4.21 - 3.98 (m, 2H), 3.96 (d, J = 16.7 Hz, 1H), 3.82 (m, 1H), 3.68 (s, 3H), 2.98 (dd, 1H), 2.94 (dd, 1H), 2.83 (dd, 1H), 25 2.46 (dd, 1H). Anal. Calcd for C₁₅H₁₆F₃NO₄: C, 54.38; H, 4.87; N, 4.23. Found: C, 54.40; H, 4.96; N, 4.22.

Preparation 22

30 Preparation of methyl (S)-8-hydroxy-3-oxo-2-(2-phenylethyl)-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetate via enantioselective synthesis

a) 3-[N-(*tert*-Butoxycarbonyl)-N-(2-phenylethyl)amino]methyl-4-bromoanisole

2-Phenethylamine (19.0 mL, 150 mmole) was added all at once to a solution of 4-bromo-3-bromomethylanisole (14.0 g, 50.0 mmole) in anhydrous THF (200 mL) at RT. 35 After 18 hr the mixture was concentrated. The residue was dissolved in 2 M NaOH (300 mL) and extracted with CH₂Cl₂ (3 x 200 mL). The combined CH₂Cl₂ layers were dried

over MgSO_4 and concentrated. The crude material was filtered through a plug of silica gel using 50% EtOAc/hexanes as eluent. The filtrate was concentrated under reduced pressure to give a yellow oil: MS (ES) m/e 320 ($M + H$)⁺.

5 The above yellow oil was dissolved in anhydrous THF (200 mL) and di-*tert*-butyl dicarbonate (13.0 g, 60.0 mmole) was added all at once at RT. After 1 hr the solution was concentrated. Flash silica gel chromatography (10% EtOAc/hexanes) gave the title compound as an off-white solid (20.8 g, 100% from 4-bromo-3-bromomethylanisole): ¹H NMR (250 MHz, CDCl_3) δ 7.51-7.10 (m, 6H), 6.85-6.60 (m, 2H), 4.52-4.33 (m, 2H), 3.71 (s, 3H), 3.52-3.31 (m, 2H), 2.92-2.73 (m, 2H), 1.61-1.33 (m, 9H).

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b) 4-[2-[N-(*tert*-Butoxycarbonyl)-N-(2-phenylethyl)amino]methyl-4-methoxyphenyl]propionic acid

A solution of 3-[N-(*tert*-butoxycarbonyl)-N-(2-phenylethyl)amino]methyl-4-bromoanisole (20.0 g, 48.0 mmole), benzyl acrylate (23.0 g, 144 mmole), palladium acetate (540 mg, 2.40 mmole), tri-*o*-tolylphosphine (1.46 g, 4.80 mmole), and diisopropylethylamine (17.0 mL, 96.0 mmole) in propionitrile (250 mL) was deoxygenated (3x evacuation/argon purge cycles), then was heated to reflux under argon. After 48 hr the reaction was cooled to RT, filtered through a pad of celite®, and concentrated. Flash silica gel chromatography (10% EtOAc/hexane) gave a yellow oil, which was dissolved in 10% EtOAc/hexanes (100 mL) and left at 4 °C for 72 hr. The yellow precipitate was removed by filtration then the solution was concentrated to give a faint yellow oil (14.98 g, 62%): ¹H-NMR (250 MHz, CDCl_3) δ 8.00-7.85 (m, 1H), 7.61-7.01 (m, 11H), 6.85-6.76 (m, 2H), 6.75-6.67 (m, 1H), 6.32 (m, 1H), 5.22 (s, 2H), 4.60-4.41 (m, 2H), 3.75 (s, 3H), 3.52-3.20 (m, 2H), 2.93-2.71 (m, 2H), 1.55-1.33 (m, 9H).

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The above oil was dissolved in MeOH (150 mL) and 10% Pd/C (6.40 g, 6.00 mmole) was added at 0 °C. The mixture was warmed to RT, shaken under hydrogen (50 psi) for 7 hr, then was filtered through a pad of celite® to remove the catalyst. The filtrate was concentrated under reduced pressure to give the title compound as a thick yellow oil (10.35 g, 83%): ¹H-NMR (250 MHz, CDCl_3) δ 7.35-7.02 (m, 6H), 6.85-6.76 (m, 2H), 6.75-6.73 (m, 1H), 6.69-6.68 (m, 1H), 4.42-4.25 (m, 2H), 3.73 (s, 3H), 3.44-3.25 (m, 2H), 2.92-2.73 (m, 4H), 2.59-2.50 (m, 2H), 1.60-1.33 (m, 9H).

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c) (R)-1,1-Dimethylethyl[[5-methoxy-2-[3-oxo-3-[2-oxo-4-(phenylmethyl)-3-oxazolidinyl]propyl]phenyl]methyl](2-phenylethyl)carbamate

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To a solution of 4-[2-[N-(*tert*-butoxycarbonyl)-N-(2-phenylethyl)amino]methyl-4-methoxyphenyl]propionic acid (10.35 g, 25.0 mmole) in CH_2Cl_2 (125 mL) was added pyridine (2.4 mL, 30.0 mmole) then cyanuric fluoride (1.4 mL, 15.0 mmole) at RT. After 2

hr the mixture was filtered through a pad of celite®, washed with cold H₂O (100 mL) then with brine (100 mL), dried over MgSO₄, and concentrated.

To a solution of (R)-4-benzyl-2-oxazolidinone (5.30 g, 30.0 mmole) in anhydrous THF (125 mL) was added *n*-BuLi (11.0 mL, 2.5 M solution in hexanes, 27.5 mmole) at -78 °C. After 15 minutes the above acid fluoride in anhydrous THF (25 mL) was added dropwise over 5 minutes. After 1 hr the mixture was poured into 300 mL H₂O and extracted with EtOAc (3 x 200 mL). The combined EtOAc layers were dried over MgSO₄ and concentrated. Flash silica gel chromatography (30% EtOAc/hexanes) gave the title compound as a thick oil (12.12 g, 85%): ¹H-NMR (250 MHz, CDCl₃) δ 7.41-7.12 (m, 11H), 6.65 (m, 1H), 6.60 (m, 1H), 4.70-4.62 (m, 1H), 4.50-4.35 (m, 2H), 4.21-4.10 (m, 2H), 3.71(s, 3H), 3.50-2.61 (m, 10H), 1.55-1.41 (m, 9H).

d) [R-(R*, S*)]-Methyl β-[4-methoxy-2-[[[(1,1-dimethylethoxy)carbonyl](2-phenylethyl)amino]methyl]phenyl]methyl]-γ-oxo-4-(phenylmethyl)-3-oxazolidinebutanoate

To a solution of (R)-1,1-dimethylethyl[[5-methoxy-2-[3-oxo-3-[2-oxo-4-(phenylmethyl)-3-oxazolidinyl]propyl]phenyl]methyl](2-phenylethyl)carbamate (12.12 g, 21.0 mmole) in anhydrous THF (100 mL) was added lithium bis(trimethylsilyl)amide (22.0 mL, 1M in THF, 22.0 mmole) at -78 °C. After 15 minutes methyl bromoacetate (9.9 mL, 105 mmole) was added then the mixture was warmed to -20 °C. After 3 hr the mixture was poured into 200 mL H₂O and extracted with EtOAc (3 x 500 mL). The combined EtOAc layers were dried over MgSO₄ and concentrated. Flash silica gel chromatography (25% EtOAc/hexanes) gave 9.91 g of a 3:2 mixture (HPLC, 20% EtOAc/hexanes) of the title compound and (R)-1,1-Dimethylethyl[[5-methoxy-2-[3-oxo-3-[2-oxo-4-(phenylmethyl)-3-oxazolidinyl]propyl]phenyl]methyl](2-phenylethyl)carbamate respectively. This mixture was used without further purification: MS (ES) m/e 667 (M + Na)⁺.

e) Methyl (S)-8-methoxy-3-oxo-2-(2-phenylethyl)-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetate

To a solution of [R-(R*, S*)]-methyl β-[4-methoxy-2-[[[(1,1-dimethylethoxy)carbonyl](2-phenylethyl)amino]methyl]phenyl]methyl]-γ-oxo-4-(phenylmethyl)-3-oxazolidinebutanoate (9.91 g, 15.4 mmole) in THF (75 mL) was added a solution of lithium hydroxide monohydrate (646 mg, 15.4 mmole) and H₂O₂ (5.2 mL, 30 % in H₂O, 46.2 mmole) in H₂O (25 mL) at 0 °C over 10 minutes. After 1.5 hr a solution of Na₂SO₃ (9.7 g, 77 mmole) in H₂O (100 mL) was added. The mixture was acidified to pH 4 using 2 M HCl and extracted with EtOAc (3 x 200 mL). The combined EtOAc layers were dried over MgSO₄ and concentrated. The resulting residue was dissolved in 4.0 M

HCl in dioxane (75 mL). After 45 minutes the mixture was concentrated then reconcentrated from toluene (200 mL).

The above residue was dissolved in anhydrous DMF (75 mL). To this solution was added NaHCO₃ (6.50 g, 77.0 mmole) and triethylamine (4.3 mL, 30.8 mmole) at RT. The mixture was cooled to 0 °C and diphenylphosphoryl azide (5 mL, 23.1 mmole) was added. After 16 hr the mixture was concentrated. The resulting paste was dissolved in EtOAc (500 mL), washed with H₂O (2 x 300 mL), dried over MgSO₄, and concentrated. Flash silica gel chromatography (40% EtOAc/hexanes) gave the title compound (2.61 g, 33% from [R-(R*, S*)]-methyl β-[[[4-methoxy-2-[[[(1,1-dimethylethoxy)carbonyl](2-phenylethyl)amino]methyl]phenyl]methyl]-γ-oxo-4-(phenylmethyl)-3-oxazolidinebutanoate) as a clear oil: MS (ES) m/e 390 (M + Na)⁺.

f) Methyl (S)-8-hydroxy-3-oxo-2-(2-phenylethyl)-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetate

To a solution of methyl (S)-8-methoxy-3-oxo-2-(2-phenylethyl)-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetate (2.61 g, 7.1 mmole) in CH₂Cl₂ (40 mL) was added BBr₃ (21.3 mL, 1M in CH₂Cl₂, 21.3 mmole) at -20 °C. After 45 minutes the mixture was quenched with MeOH (200 mL) and concentrated. The residue was filtered through a silica gel plug using 50 % EtOAc/hexanes as eluent. The resulting orange solid was recrystallized from MeOH/H₂O to give the title compound as an off-white solid (2.16 g, 81%): MS (ES) m/e 376 (M + Na)⁺.

Example 1

Preparation of (±)-8-[3-(2-pyridylamino)-1-propyloxy]-3-oxo-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetic acid

a) Methyl (±)-8-[3-[2-(N-oxopyridyl)amino]-1-propyloxy]-3-oxo-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetate

A solution of 2-[(3-hydroxy-1-propyl)amino]pyridine-N-oxide (1.4 g, 8 mmol) in anhydrous DMF (8 mL) was added dropwise to a solution of methyl (±)-8-hydroxy-3-oxo-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetate (1.7 g, 7 mmole), triphenylphosphine (2.76 g, 11 mmol), and diethyl azodicarboxylate (2.33 mL, 14 mmole) in anhydrous DMF (4 mL) and dry THF (10 mL) at RT under argon. The resulting solution was stirred for 18 hr, then was concentrated under vacuum. Silica gel chromatography (2% - 10% CH₃OH/CH₂Cl₂) to give the title compound (1.2g): MS (ES) m/e 400.2 (M + H)⁺. Unreacted methyl (±)-8-hydroxy-3-oxo-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetate (0.4 g) was also recovered.

b) Ethyl (±)-8-[3-(2-pyridylamino)-1-propyloxy]-3-oxo-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetate

A mixture of methyl (±)-8-[3-[2-(N-oxopyridyl)amino]-1-propyloxy]-3-oxo-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetate (1.2 g, 3 mmol), 1.2 g 10% palladium on charcoal (1.2 g), cyclohexene (3 mL, 15 mmol), and ethanol (20 mL) was heated at reflux for 18 hr. The mixture was filtered and the filtrate was concentrated. The residue was purified by chromatography on silica gel (2% - 5% CH₃OH/CH₂Cl₂) to give the title compound (0.72 g, 64%) as a white foam: MS (ES) m/e 398.2 (M + H)⁺.

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c) (±)-8-[3-(2-Pyridylamino)-1-propyloxy]-3-oxo-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetic acid

A mixture of ethyl (±)-8-[3-(2-pyridylamino)-1-propyloxy]-3-oxo-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetate (0.7 g, 2 mmol), lithium hydroxide monohydrate (0.12 g, 3 mmol), 5 mL THF (5 mL), H₂O (5 mL), and MeOH (2 mL) was stirred at room temperature for 18 hr, then was then concentrated. The residue was partitioned between ethyl acetate and water, and the layers were separated. The aqueous phase was cautiously brought to pH 4 with 3 N HCl and allowed to stand. The resulting crystals were collected by filtration and dried to give the title compound (0.4 g, 65%) as a tan solid: MS m/e 370.4 (M + H)⁺. Anal. Calcd for C₂₀H₂₃N₃O₄ · 0.25 H₂O: C, 64.25; H, 6.34; N, 11.24. Found: C, 64.02; H, 6.37; N, 11.20.

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Example 2

25 Preparation of (±)-8-[3-[(4-amino-2-pyridyl)amino]-1-propyloxy]-3-oxo-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetic acid

a) Methyl (±)-8-[3-[2-(4-nitro-N-oxopyridyl)amino]-1-propyloxy]-3-oxo-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetate

30 According to the procedure of Example 1(a), except substituting 2-[(3-hydroxy-1-propyl)amino]-4-nitropyridine-N-oxide for the 2-[(3-hydroxy-1-propyl)amino]pyridine-N-oxide, the title compound was prepared as an orange foam: MS (ES) m/e 445.2 (M + H)⁺.

b) Methyl (±)-8-[3-[(4-amino-2-pyridyl)amino]-1-propyloxy]-3-oxo-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetate

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According to the procedure of Example 1(b), except substituting methyl (±)-8-[3-[2-(4-nitro-N-oxopyridyl)amino]-1-propyloxy]-3-oxo-2,3,4,5-tetrahydro-1H-2-

benzazepine-4-acetate for the methyl (\pm)-8-[3-[2-(N-oxopyridyl)amino]-1-propyloxy]-3-oxo-2,3,4,5-tetrahydro-2-benzazepine-4-acetate, the title compound was prepared as a white foam: MS (ES) m/e 399.3 (M + H)⁺.

- 5 c) (\pm)-8-[3-[(4-Amino-2-pyridyl)amino]-1-propyloxy]-3-oxo-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetic acid

According to the procedure of Example 1(c), except substituting methyl (\pm)-8-[3-[(4-amino-2-pyridyl)amino]-1-propyloxy]-3-oxo-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetate for the ethyl (\pm)-8-[3-(2-pyridylamino)-1-propyloxy]-3-oxo-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetate, the title compound was prepared as a white solid: MS (ES) m/e 385.4 (M + H)⁺. Anal. Calcd for C₂₀H₂₄N₄O₄ · 1.25 H₂O: C, 59.03; H, 6.56; N, 13.76. Found: C, 58.80; H, 6.49; N, 13.62.

Example 3

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Preparation of (\pm)-8-[3-[(4-methoxy-2-pyridyl)amino]-1-propyloxy]-3-oxo-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetic acid

- 20 a) Methyl (\pm)-8-[3-[2-(4-methoxy-N-oxopyridyl)amino]-1-propyloxy]-3-oxo-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetate

According to the procedure of Example 1(a), except substituting 2-[(3-hydroxy-1-propyl)amino]-4-methoxypyridine-N-oxide for the 2-[(3-hydroxy-1-propyl)amino]pyridine-N-oxide, the title compound was prepared as a colorless oil: MS (ES) m/e 430.3 (M + H)⁺.

- 25 b) Methyl (\pm)-8-[3-[(4-methoxy-2-pyridyl)amino]-1-propyloxy]-3-oxo-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetate

According to the procedure of Example 1(b), except substituting methyl (\pm)-8-[3-[2-(4-methoxy-N-oxopyridyl)amino]-1-propyloxy]-3-oxo-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetate for the methyl (\pm)-8-[3-[2-(N-oxopyridyl)amino]-1-propyloxy]-3-oxo-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetate, the title compound was prepared as a pale yellow oil: MS (ES) m/e 414.4 (M + H)⁺.

- 30 c) (\pm)-8-[3-[(4-Methoxy-2-pyridyl)amino]-1-propyloxy]-3-oxo-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetic acid

35 According to the procedure of Example 1(c), except substituting methyl (\pm)-8-[3-[(4-methoxy-2-pyridyl)amino]-1-propyloxy]-3-oxo-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetate for the ethyl (\pm)-8-[3-(2-pyridylamino)-1-propyloxy]-3-oxo-2,3,4,5-tetrahydro-

1H-2-benzazepine-4-acetate, the title compound was prepared as an off-white solid: MS (ES) m/e 400.3 (M + H)⁺. Anal. Calcd for C₂₁H₂₅N₃O₅ · 0.75 H₂O: C, 61.08; H, 6.47; N, 10.18. Found: C, 61.15; H, 6.20; N, 10.12.

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Example 4Preparation of (±)-8-[3-(2-pyridylamino)-1-propyloxy]-2-methyl-3-oxo-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetic acid

- 10 a) Methyl (±)-8-[3-[2-(N-oxopyridyl)amino]-1-propyloxy]-2-methyl-3-oxo-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetate

A solution of 2-[(3-hydroxy-1-propyl)amino]pyridine-N-oxide (252.3 mg, 1.5 mmole) and diethyl azodicarboxylate (0.24 mL, 1.5 mmole) in anhydrous DMF (7.5 mL) was added slowly dropwise to a solution of methyl (±)-8-hydroxy-2-methyl-3-oxo-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetate (197.5 mg, 0.75 mmole) and triphenylphosphine (413.1 mg, 1.58 mmole) in anhydrous DMF (7.5 mL) at RT. The addition required 15 min, and was mildly exothermic. After 2 hr, the reaction was concentrated and the residue was reconcentrated from xylenes. Silica gel chromatography (2:2:1 EtOAc/CHCl₃/MeOH) gave the R_f 0.48 (TLC in 2:2:1 EtOAc/CHCl₃/MeOH) material as a cloudy, nearly colorless oil. This was rechromatographed on silica gel (absolute EtOH) to afford the title compound (243.9 mg, 79%) as an off-white foam: TLC (absolute EtOH) R_f 0.33; ¹H NMR (250, CDCl₃) δ 8.12 (app. dd, 1 H), 7.10 - 7.23 (m, 1 H), 6.90 - 7.10 (m, 2 H), 6.78 (dd, J = 8.4, 2.6 Hz, 1 H), 6.45 - 6.72 (m, 3 H), 5.28 (d, J = 16.3 Hz, 1 H), 3.95 - 4.25 (m, 2 H), 3.60 - 3.90 (m, 1 H), 3.76 (d, J = 16.3 Hz, 1 H), 3.71 (s, 3 H), 3.51 (q, J = 6.4 Hz, 2 H), 2.73 - 3.15 (m, 3 H), 3.04 (s, 3 H), 2.41 (dd, J = 16.7, 5.4 Hz, 1 H), 2.05 - 2.28 (m, 2 H); MS (ES) m/e 414 (M + H)⁺.

- 20 b) Methyl (±)-8-[3-(2-pyridylamino)-1-propyloxy]-2-methyl-3-oxo-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetate

30 A mixture of methyl (±)-8-[3-[2-(N-oxopyridyl)amino]-1-propyloxy]-2-methyl-3-oxo-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetate (243.9 mg, 0.59 mmole), cyclohexene (0.60 mL, 5.9 mmole), and 10% Pd/C (63 mg, 0.06 mmole) in 2-propanol (6 mL) was heated at reflux. After 21.5 hr, the reaction was cooled to RT and filtered through celite®. The filtrate was concentrated, and the residue was reconcentrated from toluene. Silica gel chromatography (5 % MeOH in 1:1 EtOAc/CHCl₃) gave the title compound (212.8 mg, 91%) as a colorless oil: TLC (5 % MeOH in 1:1 EtOAc/CHCl₃) R_f 0.39; ¹H NMR (250, CDCl₃) δ 8.03 - 8.13 (m, 1 H), 7.35 - 7.48 (m, 1 H), 7.00 (d, J = 8.4 Hz, 1 H), 6.77 (dd, J =

8.4, 2.5 Hz, 1 H), 6.63 (d, J = 2.5 Hz, 1 H), 6.52 - 6.62 (m, 1 H), 6.40 (d, J = 8.5 Hz, 1 H), 5.27 (d, J = 16.3 Hz, 1 H), 4.62 - 4.82 (m, 1 H), 3.95 - 4.20 (m, 2 H), 3.60 - 3.90 (m, 2 H), 3.71 (s, 3 H), 3.50 (q, J = 6.3 Hz, 2 H), 2.75 - 3.15 (m, 3 H), 3.03 (s, 3 H), 2.40 (dd, J = 16.7, 5.3 Hz, 1 H), 2.00 - 2.22 (m, 2 H); MS (ES) m/e 398 (M + H)⁺.

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c) (±)-8-[3-(2-Pyridylamino)-1-propyloxy]-2-methyl-3-oxo-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetic acid

1.0 N LiOH (0.80 mL, 0.80 mmole) was added to a solution of methyl (±)-8-[3-(2-pyridylamino)-1-propyloxy]-2-methyl-3-oxo-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetate (207.5 mg, 0.52 mmole) in THF (2.6 mL) and H₂O (1.8 mL) at RT. The initially cloudy solution became homogeneous within 1 min. After 18 hr, the reaction was acidified with TFA (0.12 mL, 1.56 mmole) and concentrated. ODS chromatography (20% CH₃CN/H₂O containing 0.1% TFA), concentration, and lyophilization gave the title compound (252.4 mg, 83%) as a light yellow, hygroscopic solid: HPLC (PRP-1®, 20% CH₃CN/H₂O containing 0.1% TFA) K' = 2.4; ¹H NMR (400 MHz, CD₃OD) δ 7.83 - 7.93 (m, 1 H), 7.76 - 7.83 (m, 1 H), 7.00 - 7.11 (m, 2 H), 6.83 - 6.91 (m, 1 H), 6.80 (dd, J = 8.4, 2.6 Hz, 1 H), 6.76 (d, J = 2.6 Hz, 1 H), 5.30 (d, J = 16.5 Hz, 1 H), 4.05 - 4.18 (m, 2 H), 3.94 (d, J = 16.5 Hz, 1 H), 3.77 - 3.90 (m, 1 H), 3.57 (t, J = 6.8 Hz, 2 H), 3.03 (dd, J = 17.0, 4.2 Hz, 1 H), 2.99 (s, 3 H), 2.83 (dd, J = 17.0, 9.1 Hz, 1 H), 2.72 (dd, J = 17.0, 13.5 Hz, 1 H), 2.44 (dd, J = 17.0, 4.7 Hz, 1 H), 2.11 - 2.23 (m, 2 H); MS (ES) m/e 384 (M + H)⁺. Anal. Calcd for C₂₁H₂₅N₃O₄ · 1.5 CF₃CO₂H · 1.5 H₂O: C, 49.57; H, 5.11; N, 7.23. Found: C, 49.65; H, 4.95; N, 7.15.

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Example 5

Preparation of (±)-8-[3-(2-imidazolylamino)-1-propyloxy]-3-oxo-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetic acid

The title compound is prepared generally following the procedures detailed in Examples 1-4.

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Example 6Preparation of (±)-8-[3-[2-(1,4,5,6-tetrahydropyrimidinyl)amino]-1-propyloxy]-3-oxo-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetic acid

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a) Methyl (±)-8-[3-(*tert*-butoxycarbonylamino)-1-propyloxy]-3-oxo-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetate

A solution of 3-[(*tert*-butoxycarbonyl)amino]-1-propanol (0.14 g, 0.8 mmol) and diethyl azodicarboxylate (0.13 mL, 0.8 mmole) in anhydrous DMF (2 mL) was added dropwise to a solution of methyl (±)-8-hydroxy-3-oxo-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetate (0.10 g, 0.4 mmole) and triphenylphosphine (0.21 g, 0.8 mmol) in anhydrous DMF (1.4 mL) and dry THF (2 mL) at RT under argon. The resulting solution was stirred for 18 hr, then was concentrated under vacuum. Silica gel chromatography (1% - 3% MeOH/CH₂Cl₂) gave the title compound (0.11 g): MS (ES) m/e 407.3 (M + H)⁺.

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b) Methyl (±)-8-(3-amino-1-propyloxy)-3-oxo-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetate, trifluoroacetate salt

A solution of methyl (±)-8-[3-(*tert*-butoxycarbonylamino)-1-propyloxy]-3-oxo-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetate (0.70 g) in CH₂Cl₂ (7 mL) and TFA (2 mL) was stirred under argon at 0°C for 1 hr, then was concentrated to give the title compound (0.75 g, 100%) as a colorless glass: MS (ES) m/e 321.4 (M + H)⁺.

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c) Methyl (±)-8-[3-(pyrimidin-2-ylamino)-1-propyloxy]-3-oxo-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetate

A mixture of methyl (±)-8-(3-amino-1-propyloxy)-3-oxo-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetate trifluoroacetate salt (0.75 g, 2 mmol), 2-bromopyrimidine (0.5 g, 3 mmol), NaHCO₃ (1.4 g, 17 mmol), and EtOH (10 mL) was heated to reflux. After 24 hr, the mixture was filtered and the insoluble material was washed with MeOH. The filtrate and washings were combined and concentrated, and the residue was purified by chromatography on silica gel (1%-6% MeOH/CH₂Cl₂) to give the title compound (0.54 g, 82 %) as a white foam: MS (ES) m/e 385.5 (M + H)⁺.

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d) (±)-8-[3-[(1,4,5,6-Tetrahydropyrimidin-2-yl)amino]-1-propyloxy]-3-oxo-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetic acid

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A mixture of methyl (±)-8-[3-(pyrimidin-2-ylamino)-1-propyloxy]-3-oxo-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetate (0.36 g, 0.94 mmol), 4 M HCl in dioxane (0.25 mL, 1 mmol), 10% palladium on charcoal (0.24 g, 0.24 mmol), and MeOH (5 mL) was stirred

under a balloon of hydrogen. After 18 hr, the mixture was filtered and the filtrate was concentrated. The residue was partitioned between EtOAc and aqueous K_2CO_3 . A solid precipitated, which was collected by filtration and dried to give the title compound as a white solid: MS m/e 375.4 ($M + H$)⁺. Anal. Calcd for $C_{19}H_{26}N_4O_4 \cdot 2.5 H_2O$: C, 54.40; H, 7.45; N, 13.35. Found: C, 54.68; H, 7.12; N, 13.39.

Example 7

Preparation of (±)-8-[3-(6-amino-2-pyridylamino)-1-propyloxy]-3-oxo-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetic acid

The title compound is prepared generally following the procedures detailed in Examples 1-4.

Example 8

Preparation of (±)-8-[2-[6-(methylamino)pyridyl]ethoxy]-3-oxo-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetic acid

a) Methyl (±)-8-[2-[6-(methylamino)pyridin-2-yl]-1-ethoxy]-3-oxo-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetate

According to the procedure of Example 1(a), except substituting 6-(methylamino)-2-pyridylethanol for the 2-[(3-hydroxy-1-propyl)amino]pyridine-N-oxide, the title compound was prepared as a white foam: MS (ES) m/e 384 ($M + H$)⁺.

b) (±)-8-[2-[6-(Methylamino)pyridin-2-yl]-1-ethoxy]-3-oxo-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetic acid

According to the procedure of Example 1(c), except substituting methyl (±)-8-[2-[6-(methylamino)pyridin-2-yl]-1-ethoxy]-3-oxo-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetate methyl for the ethyl (±)-8-[3-[2-pyridylamino-1-propyloxy]-3-oxo-2,3,4,5-tetrahydro-1H-2-benzodiazepine-4-acetate, the title compound was prepared as a white solid: MS (ES) m/e 370 ($M + H$)⁺.

Example 9Preparation of (±)-8-[2-(2-benzimidazolyl)ethoxy]-3-oxo-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetic acid

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a) Methyl (±)-8-[2-(benzimidazol-2-yl)-1-ethoxy]-3-oxo-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetate

According to the procedure of Example 1(a), except substituting 2-(benzimidazol-2-yl)-1-ethanol for the 2-[(3-hydroxy-1-propyl)amino]pyridine-N-oxide, the title compound was prepared as an off white solid: MS (ES) m/e 394.4 (M + H)⁺, 416.3 (M + Na)⁺.

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b) (±)-8-[2-(Benzimidazol-2-yl)-1-ethoxy]-3-oxo-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetic acid

According to the procedure of Example 1(c), except substituting methyl (±)-8-[2-(benzimidazol-2-yl)-1-ethoxy]-3-oxo-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetate for the ethyl (±)-8-[3-(2-pyridylamino)-1-propyloxy]-3-oxo-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetate, the title compound was prepared as a white powder: MS (ES) m/e 380.4 (M + H)⁺, 402.3 (M + Na)⁺.

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Example 10Preparation of (±)-8-[2-(4-aza-2-benzimidazolyl)ethoxy]-3-oxo-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetic acid

The title compound is prepared generally following the procedures detailed in Example 9.

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Example 11Preparation of (±)-3-oxo-8-[3-(pyridin-2-ylamino)-1-propyloxy]-2-(2,2,2-trifluoroethyl)-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetic acid

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a) Methyl (±)-3-oxo-8-[3-(1-oxopyridin-2-ylamino)-1-propyloxy]-2-(2,2,2-trifluoroethyl)-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetate

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A solution of 2-[(3-hydroxy-1-propyl)amino]pyridine-N-oxide (252.3 mg, 1.5 mmole) and diethyl azodicarboxylate (0.24 mL, 1.5 mmole) in anhydrous DMF (7.5 mL) was added slowly dropwise over 3 - 4 min to a solution of methyl (±)-8-hydroxy-3-oxo-2-

(2,2,2-trifluoroethyl)-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetate (248.5 mg, 0.75 mmole) and triphenylphosphine (413.1 mg, 1.58 mmole) in anhydrous DMF (7.5 mL) at RT. After 17 hr, the reaction was concentrated and the residue was reconstituted from xylenes/CHCl₃. Silica gel chromatography (gradient: EtOAc (500 mL) then 5%

- 5 MeOH/CHCl₃) gave the title compound (253.6 mg, 70%) as an off-white foam: ¹H NMR (250, CDCl₃) δ 8.11 (dd, J = 6.4, 1.4 Hz, 1 H), 7.10 - 7.23 (m, 1 H), 6.93 - 7.10 (m, 2 H), 6.81 (dd, J = 8.4, 2.6 Hz, 1 H), 6.45 - 6.70 (m, 3 H), 5.34 (d, J = 16.7 Hz, 1 H), 3.75 - 4.30 (m, 6 H), 3.71 (s, 3 H), 3.51 (q, J = 6.4 Hz, 2 H), 2.80 - 3.15 (m, 3 H), 2.46 (dd, J = 16.8, 5.5 Hz, 1 H), 2.07 - 2.28 (m, 2 H); MS (ES) m/e 482.2 (M + H)⁺.

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b) Methyl (±)-3-oxo-8-[3-(pyridin-2-ylamino)-1-propyloxy]-2-(2,2,2-trifluoroethyl)-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetate

- A mixture of methyl (±)-3-oxo-8-[3-(1-oxopyridin-2-ylamino)-1-propyloxy]-2-(2,2,2-trifluoroethyl)-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetate (253.6 mg, 0.53 mmole), cyclohexene (0.54 mL, 5.3 mmole), palladium black (11.3 mg, 0.11 mmole), and isopropanol (5.3 mL) was heated to reflux. After 0.5 hr, 10% Pd/C (28.2 mg, 0.03 mmole) was added, and after 14.5 hr, Pd black (11.3 mg, 0.11 mmole) and cyclohexene (0.27 mL, 2.65 mmole) were added. After an additional 48 hr, the reaction was hot-filtered through celite®, and the filter pad was washed with hot 1:1 MeOH/CHCl₃. Concentration and reconstitution from xylenes left a yellow oil. Silica gel chromatography (5% MeOH in 1:1 EtOAc/CHCl₃) gave the title compound (194.0 mg, 79%) as a light yellow oil: TLC (5% MeOH in 1:1 EtOAc/CHCl₃) R_f 0.53; ¹H NMR (250, CDCl₃) δ 8.08 (dd, J = 5.0, 1.0 Hz, 1 H), 7.37 - 7.48 (m, 1 H), 7.02 (d, J = 8.4 Hz, 1 H), 6.79 (dd, J = 8.4, 2.5 Hz, 1 H), 6.63 (d, J = 2.5 Hz, 1 H), 6.52 - 6.62 (m, 1 H), 6.40 (d, J = 8.4 Hz, 1 H), 5.34 (d, J = 16.6 Hz, 1 H), 4.60 - 4.80 (m, 1 H), 3.75 - 4.30 (m, 6 H), 3.71 (s, 3 H), 3.50 (q, J = 6.4 Hz, 2 H), 2.80 - 3.15 (m, 3 H), 2.46 (dd, J = 16.8, 5.4 Hz, 1 H), 2.00 - 2.25 (m, 2 H); MS (ES) m/e 466 (M + H)⁺.

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c) (±)-3-Oxo-8-[3-(pyridin-2-ylamino)-1-propyloxy]-2-(2,2,2-trifluoroethyl)-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetic acid

- 1.0 N LiOH (0.44 mL, 0.44 mmole) was added to a solution of methyl (±)-8-[3-(2-pyridylamino)-1-propyloxy]-3-oxo-2-(2,2,2-trifluoroethyl)-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetate (159.5 mg, 0.34 mmole) in THF (1.7 mL) and H₂O (1.3 mL) at RT. The yellow, cloudy reaction became homogeneous within 10 min. After 24 hr, the reaction was concentrated to dryness and the yellow residue was dissolved in H₂O (4 mL). The solution was filtered, then was carefully neutralized (pH ≈ 7) with 1.0 N HCl. The precipitate was collected, washed with plenty of H₂O, and dried in high vacuum at 40 - 45

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°C to afford the title compound (130.0 mg, 83%) as an off-white solid: HPLC (PRP-1®, 25% CH₃CN/H₂O containing 0.1% TFA) $k' = 3.1$; ¹H NMR (400 MHz, DMSO-d₆) δ 7.91 - 8.00 (m, 1 H), 7.28 - 7.40 (m, 1 H), 7.02 (d, J = 9.2 Hz, 1 H), 6.76 - 6.87 (m, 2 H), 6.51 - 6.60 (m, 1 H), 6.39 - 6.50 (m, 2 H), 5.30 (d, J = 16.6 Hz, 1 H), 4.10 - 4.30 (m, 3 H), 4.02 (t, J = 6.3 Hz, 1 H), 3.70 - 3.82 (m, 1 H), 3.20 - 3.45 (m, 2 H, partially obscured by residual solvent signal), 2.99 (dd, 1 H), 2.59 - 2.74 (m, 2 H), 2.39 (dd, J = 16.9, 4.8 Hz, 1 H), 1.90 - 2.03 (m, 2 H); MS (ES) m/e 452 (M + H)⁺. Anal. Calcd for C₂₂H₂₄F₃N₃O₄ · 0.5 H₂O: C, 57.39; H, 5.47; N, 9.13. Found: C, 57.39; H, 5.18; N, 9.00.

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Example 12Preparation of (±)-8-[3-(4,6-dimethylpyridin-2-ylamino)-1-propyloxy]-2-methyl-3-oxo-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetic acid

15 a) Methyl (±)-8-[3-(4,6-dimethyl-1-oxopyridin-2-ylamino)-1-propyloxy]-2-methyl-3-oxo-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetate

According to the procedure of Example 1(a), except substituting 2-[(3-hydroxy-1-propyl)amino]-4,6-dimethylpyridine-N-oxide for the 2-[(3-hydroxy-1-propyl)amino]pyridine-N-oxide, the title compound was prepared as white foam: MS (ES) m/e 442.3 (M + H)⁺.

20 b) Methyl (±)-8-[3-(4,6-dimethylpyridin-2-ylamino)-1-propyloxy]-2-methyl-3-oxo-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetate

According to the procedure of Example 1(b), except substituting methyl (±)-8-[3-(4,6-dimethyl-1-oxopyridin-2-ylamino)-1-propyloxy]-2-methyl-3-oxo-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetate for the methyl (±)-8-[3-[2-(N-oxopyridyl)amino]-1-propyloxy]-3-oxo-2,3,4,5-tetrahydro-2-benzazepine-4-acetate, the title compound was prepared as a pale yellow solid: MS (ES) m/e 426.3 (M + H)⁺.

30 c) (±)-8-[3-(4,6-Dimethylpyridin-2-ylamino)-1-propyloxy]-2-methyl-3-oxo-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetic acid

According to the procedure of Example 1(c), except substituting methyl (±)-8-[3-[(4,6-dimethylpyridin-2-yl)amino]-1-propyloxy]-2-methyl-3-oxo-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetate for the ethyl (±)-8-[3-(2-pyridylamino)-1-propyloxy]-3-oxo-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetate, the title compound was prepared as a white solid: MS (ES) m/e 412.2 (M + H)⁺. Anal. Calcd for C₂₃H₂₉N₃O₄ · 0.5 HCl · 0.25 H₂O: C, 63.62; H, 6.96; N, 9.68. Found: C, 63.62; H, 6.96; N, 9.69.

Example 13Preparation of (±)-8-[2-(2-aminothiazol-4-yl)-1-ethoxy]-2-methyl-3-oxo-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetic acid

a) Methyl (±)-8-[2-(2-aminothiazol-4-yl)-1-ethoxy]-2-methyl-3-oxo-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetate

According to the procedure of Example 1(a), except substituting 2-(2-aminothiazol-4-yl)ethanol (WO 95/32710) for the 2-[(3-hydroxy-1-propyl)amino]pyridine-N-oxide, the title compound was prepared as white foam: MS (ES) m/e 390 (M + H)⁺.

b) (±)-8-[2-(2-Aminothiazol-4-yl)-1-ethoxy]-2-methyl-3-oxo-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetic acid

According to the procedure of Example 1(c) except substituting methyl (±)-8-[2-(2-aminothiazol-4-yl)-1-ethoxy]-2-methyl-3-oxo-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetate for the ethyl (±)-8-[3-(2-pyridylamino-1-propyloxy)-3-oxo-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetate, the title compound was prepared as a white solid: MS (ES) m/e 376 (M + H)⁺. Anal. Calcd for C₁₈H₂₁N₃O₄S · 1.3 CF₃CO₂H · 0.36 H₂O: C, 46.62; H, 4.38; N, 7.93. Found: C, 46.45; H, 4.57; N, 8.27.

Example 14Preparation of (±)-8-[3-(4-aminopyridin-2-ylamino)-1-propyloxy]-2-methyl-3-oxo-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetic acid

a) Methyl (±)-8-[3-(4-nitro-1-oxopyridin-2-ylamino)-1-propyloxy]-2-methyl-3-oxo-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetate

According to the procedure of Example 1 (a), except substituting 2-[(3-hydroxy-1-propyl)amino]-4-nitropyridine-N-oxide for the 2-[(3-hydroxy-1-propyl)amino]pyridine-N-oxide and substituting methyl (±)-8-hydroxy-2-methyl-3-oxo-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetate for the methyl (±)-8-hydroxy-3-oxo-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetate, the tile compound was prepared: MS (ES) m/e 459 (M + H)⁺.

b) Methyl (±)-8-[3-(4-aminopyridin-2-ylamino)-1-propyloxy]-2-methyl-3-oxo-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetate

According to the procedure of Example 1(b), except substituting methyl (±)-8-[3-(4-nitro-1-oxopyridin-2-ylamino)-1-propyloxy]-2-methyl-3-oxo-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetate for the methyl (±)-8-[3-(4-nitro-N-oxopyridin-2-ylamino)-1-propyloxy]-3-oxo-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetate, the title compound was prepared as a white foam: MS (ES) m/e 413 (M + H)⁺.

b) (±)-8-[3-(4-Aminopyridin-2-ylamino)-1-propyloxy]-2-methyl-3-oxo-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetic acid

According to the procedure of Example 1(c), except substituting methyl (±)-8-[3-(4-aminopyridin-2-ylamino)-1-propyloxy]-2-methyl-3-oxo-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetate for the ethyl (±)-8-[3-[2-pyridylamino)-1-propyloxy]-3-oxo-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetate, the title compound was prepared as a white solid: MS (ES) m/e 399 (M + H)⁺. Anal. Calcd for C₂₁H₂₆N₄O₄ · 1.5 CF₃CO₂H · 0.125 H₂O: C, 50.62; H, 4.91; N, 9.83. Found: C, 50.63; H 5.26; N, 9.90.

Example 15

20 Preparation of (±)-8-[3-(Pyrimidin-2-ylamino)-1-propyloxy]-3-oxo-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetic acid

A mixture of methyl (±)-8-[3-(pyrimidin-2-ylamino)-1-propyloxy]-3-oxo-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetate (0.071 g, 0.18 mmol) and lithium hydroxide monohydrate (0.009 g, 2 mmol) in THF (5 mL) and H₂O (2 mL) was stirred at room temperature for 18 hr, then was concentrated. The residue was dissolved in H₂O and the pH was adjusted to 4 with 3 N HCl. The resulting solid was collected by filtration and dried to give the title compound (0.05 g, 73%) as a white solid: MS m/e 371.4 (M + H)⁺. Anal. Calcd for C₁₉H₂₂N₄O₄ · 0.5 H₂O: C, 60.15; H, 6.11; N, 14.77. Found: C, 60.14, H, 6.06; N, 14.71.

Example 16Preparation of (R)-8-[3-[(4-amino-2-pyridyl)amino]-1-propyloxy]-3-oxo-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetic acid

5

a) Methyl (R)-8-[3-[2-(4-nitro-1-oxopyridyl)amino]-1-propyloxy]-3-oxo-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetate

According to the procedure of Example 1(a), except substituting 2-[(3-hydroxy-1-propyl)amino]-4-nitropyridine-N-oxide for the 2-[(3-hydroxy-1-propyl)amino]pyridine-N-oxide, the title compound was prepared as an orange foam: MS (ES) m/e 445.3 (M + H)⁺.

10

b) Methyl (R)-8-[3-[(4-amino-2-pyridyl)amino]-1-propyloxy]-3-oxo-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetate

According to the procedure of Example 1(b), except substituting methyl (R)-8-[3-[2-(4-amino-N-oxopyridyl)amino]-1-propyloxy]-3-oxo-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetate for the methyl (±)-8-[3-[2-(N-oxopyridyl)amino]-1-propyloxy]-3-oxo-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetate, the title compound was prepared as a white foam: MS (ES) m/e 399.4 (M + H)⁺.

15

20 c) (R)-8-[3-[(4-amino-2-pyridyl)amino]-1-propyloxy]-3-oxo-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetic acid

According to the procedure of Example 1(c), except substituting methyl (R)-8-[3-[(4-amino-2-pyridyl)amino]-1-propyloxy]-3-oxo-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetate for the ethyl (±)-8-[3-(2-pyridylamino)-1-propyloxy]-3-oxo-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetate, the title compound was prepared as an off-white solid: $[\alpha]_D^{23} +74.97^\circ$ (c 1.45, MeOH); MS (ES) m/e 385.4 (M + H)⁺. Anal. Calcd for C₂₀H₂₄N₄O₄ · HCl · 1.5 H₂O: C, 53.63; H, 6.30; N, 12.50. Found: C, 53.87; H, 6.13; N, 12.42.

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Example 17Preparation of (S)-8-[3-[(4-amino-2-pyridyl)amino]-1-propyloxy]-3-oxo-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetic acid

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a) Methyl (S)-8-[3-[2-(4-nitro-N-oxopyridyl)amino]-1-propyloxy]-3-oxo-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetate

According to the procedure of Example 1(a), except substituting 2-[(3-hydroxy-1-propyl)amino]-4-nitropyridine-N-oxide for the 2-[(3-hydroxy-1-propyl)amino]pyridine-N-oxide, the title compound was prepared as an orange foam: MS (ES) m/e 445.3 (M + H)⁺.

10

b) Methyl (S)-8-[3-[(4-amino-2-pyridyl)amino]-1-propyloxy]-3-oxo-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetate

According to the procedure of Example 1(b), except substituting methyl (S)-8-[3-[2-(4-amino-N-oxopyridyl)amino]-1-propyloxy]-3-oxo-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetate for the methyl (±)-8-[3-[2-(N-oxopyridyl)amino]-1-propyloxy]-3-oxo-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetate, the title compound was prepared as a white foam: MS (ES) m/e 399.4 (M + H)⁺.

15

c) (S)-8-[3-[(4-amino-2-pyridyl)amino]-1-propyloxy]-3-oxo-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetic acid

According to the procedure of Example 1(c), except substituting methyl (S)-8-[3-[(4-amino-2-pyridyl)amino]-1-propyloxy]-3-oxo-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetate for the ethyl (±)-8-[3-(2-pyridylamino)-1-propyloxy]-3-oxo-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetate, the title compound was prepared as an off-white solid: $[\alpha]_D^{23}$ -77.5° (c 1.45, MeOH); MS (ES) m/e 385.4 (M + H)⁺. Anal. Calcd for C₂₀H₂₄N₄O₄ · 1.125 H₂O: C, 59.36; H, 6.54; N, 13.84. Found: C, 59.31; H, 6.74; N, 13.73.

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Example 18

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Preparation of Ethyl (±)-8-[3-(2-pyridylamino)-1-propyloxy]-2-methyl-3-oxo-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetate

a) Ethyl (±)-8-[3-(2-pyridylamino)-1-propyloxy]-2-methyl-3-oxo-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetate

35

A solution of (±)-8-[3-[(4-amino-2-pyridyl)amino]-1-propyloxy]-3-oxo-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetic acid (0.27 g, 0.7 mmol) and 4 M HCl in dioxane (0.2

mL, .8 mmol) in ethanol (10 mL) was heated to reflux. After 72 hr, the reaction was concentrated and the residue was partitioned between EtOAc and aqueous K_2CO_3 . The organic phase was washed with brine, dried ($MgSO_4$), and concentrated. The residue was dissolved in toluene (5 mL) and triethylamine (0.35 mL, 2.5 mmol), and the resulting solution was heated to reflux. After 18 hr, the reaction was concentrated under vacuum to give the title compound (0.20 g, 69%) as a tan foam: MS (ES) m/e 413.4 ($M + H$)⁺. Anal. Calcd for $C_{22}H_{28}N_4O_4 \cdot 0.25 H_2O$: C, 63.37; H, 6.89; N, 13.44. Found: C, 63.32; H, 7.17; N, 13.05.

Example 19

Preparation of (±)-8-[3-[(2-imidazolin-2-yl)amino]-1-propyloxy]-2-methyl-3-oxo-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetic acid

a) Preparation of methyl(±)-8-[3-(4-nitrobenzyloxycarbonylamino)-1-propyloxy]-2-methyl-3-oxo-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetate

According to the procedure of Example 1(a), except substituting 3-(4-nitrobenzyloxycarbonylamino)-1-propanol for the 2-[(3-hydroxy-1-propyl)amino]pyridine-N-oxide, and substituting methyl (±)-8-hydroxy-2-methyl-3-oxo-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetate for the methyl (±)-8-hydroxy-3-oxo-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetate, the title compound was prepared as a colorless oil: MS (ES) m/e 500.3 ($M + H$)⁺.

b) Methyl (±)-8-[3-amino-1-propyloxy]-2-methyl-3-oxo-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetate

A mixture of methyl (±)-8-[3-(4-nitrobenzyloxycarbonylamino)-1-propyloxy]-2-methyl-3-oxo-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetate (1.4 g, 3 mmol), 10% palladium on charcoal (0.55g, 0.6 mmol), and EtOH (20 mL) was stirred at RT under a balloon of hydrogen. After 18 hr, the mixture was filtered and the filtrate was concentrated to give the title compound (0.89g, 99%) as a tan solid: MS (ES) m/e 321.4 ($M + H$)⁺.

c) Methyl(±)-8-[3-[(2-imidazolin-2-yl)amino]-1-propyloxy]-2-methyl-3-oxo-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetate

A mixture of methyl (±)-8-[3-amino-1-propyloxy]-2-methyl-3-oxo-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetate (0.3 g, 1 mmol), 2-methylthioimidazoline (0.46g, 2 mmol), diisopropylethylamine (0.42 mL, 2 mmol) and dimethylacetamide (3 mL) was heated to 100°C under argon. After 2 hr, the reaction was concentrated under vacuum and the residue was partitioned between $CHCl_3$ and H_2O . The organic phase was dried

(MgSO₄) and concentrated, and the residue was purified by preparative HPLC to give the title compound (0.24g, 51%) as a yellow oil: MS (ES) m/e 389.4 (M + H)⁺.

- 5 d) (±)-8-[3-[(2-Imidazolin-2-yl)amino]-1-propyloxy]-2-methyl-3-oxo-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetic acid

Methyl(±)-8-[3-[(2-imidazolin-2-yl)amino]-1-propyloxy]-2-methyl-3-oxo-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetate was saponified according to the procedure of Example 1(c). Purification by preparative HPLC gave the title compound as a white solid: MS (ES) m/e 375.4 (M + H)⁺. Anal. Calcd for C₂₁H₂₆N₄O₄ · 1.96 CF₃CO₂H: C, 46.08; H, 4.73; N, 9.39; Found: C, 46.37; H, 4.53; N, 9.01.

10

Example 20

- 15 Preparation of (±)-8-[3-[(4,5,6,7-tetrahydro-1H-2-diazepin-2-yl)amino]-1-propyloxy]-2-methyl-3-oxo-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetic acid

- a) Methyl (±)-8-[3-[(2-diazepin-2-yl)amino]-1-propyloxy]-2-methyl-3-oxo-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetate

According to the procedure of Example 19(c), except substituting 2-methylthio-1,3-diazepine for the 2-methylthioimidazoline, the title compound was prepared: MS (ES) m/e 417.4 (M + H)⁺.

20

- b) (±)-8-[3-[(2-Diazepin-2-yl)amino]-1-propyloxy]-2-methyl-3-oxo-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetic acid

According to the procedure of Example 19(d), except substituting methyl (±)-8-[3-[(2-diazepin-2-yl)amino]-1-propyloxy]-2-methyl-3-oxo-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetate for the methyl(±)-8-[3-[(2-imidazolin-2-yl)amino]-1-propyloxy]-2-methyl-3-oxo-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetate the title compound was prepared: MS (ES) m/e 403.4 (M + H)⁺.

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Example 21Preparation of (±)-3-oxo-8-[3-(4-methylpyridin-2-ylamino)-1-propyloxy]-2-(2,2,2-trifluoroethyl)-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetic acid

- 5 a) Methyl (±)-3-oxo-8-[3-(4-methyl-1-oxopyridin-2-ylamino)-1-propyloxy]-2-(2,2,2-trifluoroethyl)-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetate

Following the procedure of Example 1(a), except substituting 2-[(3-hydroxy-1-propyl)amino]-4-methylpyridine-N-oxide for the 2-[(3-hydroxy-1-propyl)amino]pyridine-N-oxide, and substituting methyl(±)-3-oxo-8-hydroxy-2-(2,2,2-trifluoroethyl)-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetate for the methyl (±)-8-hydroxy-3-oxo-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetate, the title compound was prepared: MS (ES) m/e 496.3 (M + H)⁺.

- 15 b) Methyl(±)-3-oxo-8-[3-(4-methylpyridin-2-ylamino)-1-propyloxy]-2-(2,2,2-trifluoroethyl)-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetate

Following the procedure of Example 1(b), except substituting methyl(±)-3-oxo-8-[3-(4-methyl-1-oxopyridin-2-ylamino)-1-propyloxy]-2-(2,2,2-trifluoroethyl)-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetate for the methyl (±)-8-[3-[2-(N-oxopyridyl)amino]-1-propyloxy]-3-oxo-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetate, the title compound was prepared: MS (ES) m/e 480.2 (M + H)⁺.

- c) (±)-3-Oxo-8-[3-(4-methylpyridin-2-ylamino)-1-propyloxy]-2-(2,2,2-trifluoroethyl)-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetic acid

Following the procedure of Example 1(c), except substituting methyl(±)-3-oxo-8-[3-(4-methylpyridin-2-ylamino)-1-propyloxy]-2-(2,2,2-trifluoroethyl)-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetate for the ethyl (±)-8-[3-(2-pyridylamino)-1-propyloxy]-3-oxo-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetate, the title compound was prepared: MS (ES) m/e 466.2 (M + H)⁺. Anal. Calcd for C₂₃H₂₆F₃N₃O₄ · 0.5 H₂O: C, 58.22; H, 5.74; N, 8.86. Found: C, 58.54; H, 5.58; N, 8.64.

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Example 22

Preparation of (±)-3-oxo-8-[3-[N-(pyridin-2-yl)-N-(*tert*-butoxycarbonyl)amino]-1-propyloxy]-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetic acid (a) Methyl (±)-8-[3-[N-(pyridin-2-yl)-N-(*tert*-butoxycarbonyl)amino]-1-propyloxy]-3-oxo-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetic acid

According to the procedure of Example 1(b), except substituting methyl (±)-8-[3-[N-(1-oxopyridin-2-yl)-N-(*tert*-butoxycarbonyl)amino]-1-propyloxy]-3-oxo-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetic acid for the methyl (±)-8-[3-[2-(N-oxopyridyl)amino]-1-propyloxy]-3-oxo-2,3,4,5-tetrahydro-2-benzazepine-4-acetate, the title compound was prepared as a white foam: MS (ES) m/e 484.4 (M + H)⁺.

(b) (±)-3-oxo-8-[3-[N-pyridin-2-yl)-N-(*tert*-butoxycarbonyl)amino]-1-propyloxy]-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetic acid

According to the procedure of Example 1 (c), except substituting methyl (±)-8-[3-[N-(pyridin-2-yl)-N-(*tert*-butoxycarbonyl)amino]-1-propyloxy]-3-oxo-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetic acid for the ethyl (±)-8-[3-(2-pyridylamino)-1-propyloxy]-3-oxo-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetate, the title compound was prepared as a white powder: MS (ES) m/e 470.4 (M + H)⁺. Anal. Calcd for C₂₅H₃₀NaN₃O₆ · 3.25 H₂O: C, 54.59; H, 6.69; N, 7.64. Found: C, 54.47; H, 6.32; N, 7.95.

Example 23

Preparation of (±)-8-[3-[N-(1-oxopyridin-2-yl)-N-(*tert*-butoxycarbonyl)amino]-1-propyloxy]-3-oxo-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetic acid

(a) (±)-8-[3-[N-(1-oxopyridin-2-yl)-N-(*tert*-butoxycarbonyl)amino]-1-propyloxy]-3-oxo-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetic acid

According to the procedure of Example 1 (c), except substituting methyl(±)-8-[3-[N-(1-oxopyridin-2-yl)-N-(*tert*-butoxycarbonyl)amino]-1-propyloxy]-3-oxo-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetate for the ethyl (±)-8-[3-(2-pyridylamino)-1-propyloxy]-3-oxo-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetate, the title compound was prepared as a white powder: ¹H NMR (400 MHz, DMSO-d₆) δ 6.6-8.3 (m, 8 H), 3.7-4.6 (m, 3 H), 3.3-3.6 (m, 5 H), 1.8-3.0 (m, 5 H), 1.6 (s, 6 H), 1.3 (s, 3 H); MS (ES) m/e 486.4 (M + H)⁺.

Example 24Preparation of (±)-3-oxo-8-[3-[N-(pyridin-2-yl)-N-(*tert*-butoxycarbonyl)amino]-1-propyloxy]-2-(4-trifluoromethylbenzyl)-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetic acid

- 5 (a) Methyl (±)-3-oxo-8-[3-[N-(1-oxopyridin-2-yl)-N-(*tert*-butoxycarbonyl)amino]-1-propyloxy]-2-(4-trifluoromethylbenzyl)-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetate

A solution of methyl (±)-8-[3-[N-(1-oxopyridin-2-yl)-N-(*tert*-butoxycarbonyl)amino]-1-propyloxy]-3-oxo-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetic acid (0.4 g, 0.8 mmol) in DMF (5 mL) was cooled to -20°C (CCl₄/dry ice bath), and
 10 (TMS)₂NLi (1.0 M solution in THF, 0.9 mL, 0.9 mmol) was added dropwise. After 10 min a solution of 4-trifluoromethylbenzyl bromide (0.211 g, 0.88 mmol) in DMF (0.5 mL) was added. The solution was stirred under an argon atmosphere at -20°C for 10 min then at RT for 18 h. The solution was concentrated, and the residue was taken up in EtOAc and washed successively with 5% NaHCO₃ (2 x), H₂O (1 x), 5% citric acid (2 x), H₂O (1 x),
 15 and brine (1 x). The EtOAc layer was dried (MgSO₄) and concentrated to give the title compound (0.42 g, 80%): MS (ES) m/e 658.3 (M + H)⁺.

- (b) Methyl (±)-3-oxo-8-[3-[N-(pyridin-2-yl)-N-(*tert*-butoxycarbonyl)amino]-1-propyloxy]-2-(4-trifluoromethylbenzyl)-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetate

20 According to the procedure of Example 1(b), except substituting methyl (±)-3-oxo-8-[3-[N-(1-oxopyridin-2-yl)-N-(*tert*-butoxycarbonyl)amino]-1-propyloxy]-2-(4-trifluoromethylbenzyl)-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetate for the ethyl (±)-8-[3-[2-(N-oxopyridyl)amino]-1-propyloxy]-3-oxo-2,3,4,5-tetrahydro-2-benzazepine-4-acetate, the title compound (0.321 g, 78%) was prepared as a clear oil: MS (ES) m/e 642.3
 25 (M + H)⁺.

- (c) (±)-3-Oxo-8-[3-[N-(pyridin-2-yl)-N-(*tert*-butoxycarbonyl)amino]-1-propyloxy]-2-(4-trifluoromethylbenzyl)-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetic acid

30 According to the procedure of Example 1(c), except substituting methyl (±)-3-oxo-8-[3-[N-(pyridin-2-yl)-N-(*tert*-butoxycarbonyl)amino]-1-propyloxy]-2-(4-trifluoromethylbenzyl)-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetate for the ethyl (±)-8-[3-(2-pyridylamino)-1-propyloxy]-3-oxo-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetate, the title compound was prepared as an off-white solid: MS (ES) m/e 628.4 (M + H)⁺. Anal. Calcd for C₃₃H₃₆F₃N₃O₆ · 0.5 H₂O: C, 62.25; H, 5.86; N, 6.60. Found: C,
 35 62.01; H, 5.92; N, 6.81.

Example 25Preparation of (±)-3-oxo-8-[3-(pyridin-2-ylamino)-1-propyloxy]-2-(4-trifluoromethylbenzyl)-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetic acid

(a) (±)-3-Oxo-8-[3-(pyridin-2-ylamino)-1-propyloxy]-2-(4-trifluoromethylbenzyl)-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetic acid

(±)-3-Oxo-8-[3-[N-(pyridin-2-yl)-N-(*tert*-butoxycarbonyl)amino]-1-propyloxy]-2-(4-trifluoromethylbenzyl)-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetic acid (0.158 g, 0.25 mmol) was treated with 4 M HCl in dioxane (3 mL) at RT for 1 h, then the solution was concentrated. ODS chromatography (gradient 5-60% CH₃CN/H₂O containing 0.1% TFA over 1 h), concentration and lyophilization gave the title compound (0.117 g, 82%): MS (ES) *m/e* 528.4 (M + H)⁺. Anal. Calcd for C₂₈H₂₈N₃O₄ · 1 CF₃CO₂H · 1.5 H₂O: C, 53.89; H, 4.82; N, 6.28. Found: C, 53.55; H, 4.55; N, 6.04.

Example 26Preparation of (±)-2-methyl-3-oxo-8-[3-[N-(pyridin-2-yl)-N-(methylamino)]-1-propyloxy]-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetic acid

(a) Methyl (±)-8-[3-[2-(N-oxopyridyl)-N-(methylamino)-1-propyloxy]-3-oxo-2,3,4,5-tetrahydro-1H-2-methyl-benzazepine-4-acetate

A solution of methyl (±)-8-[3-[2-(N-oxopyridyl)amino]-1-propyloxy]-3-oxo-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetate (1.5 g, 3.8 mmol) in DMF (10 mL) was cooled to -20°C under an argon atmosphere, and (TMS)₂NLi (1.0 M solution in THF, 8 mL, 8 mmol) was added dropwise. The reaction was stirred at -20°C for 30 minutes, then CH₃I (0.5 mL, 7.6 mmol) was added. The solution was stirred at RT for 18 h, then was concentrated. Silica gel chromatography (10% MeOH/CH₂Cl₂) gave the title compound (1 g, 62%): MS (ES) *m/e* 428.4 (M + H)⁺.

(b) Methyl (±)-2-methyl-3-oxo-8-[3-[N-(pyridin-2-yl)-N-(methylamino)]-1-propyloxy]-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetate

According to the procedure of Example 1(b), except substituting methyl (±)-8-[3-[2-(N-oxopyridyl)-N-(methylamino)]-1-propyloxy]-3-oxo-2,3,4,5-tetrahydro-1H-2-methyl-benzazepine-4-acetate for the ethyl (±)-8-[3-(2-pyridylamino)-1-propyloxy]-3-oxo-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetate, the title compound (0.7 g, 73%) was prepared: MS (ES) *m/e* 412.4 (M + H)⁺.

(c) (±)-2-Methyl-3-oxo-8-[3-[N-(pyridin-2-yl)-N-(methyl)amino]-1-propyloxy]-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetic acid

According to the procedure of Example 1(c), except substituting methyl (±)-2-methyl-3-oxo-8-[3-[N-(pyridin-2-yl)-N-(methyl)amino]-1-propyloxy]-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetate for the ethyl (±)-8-[3-(2-pyridylamino)-1-propyloxy]-3-oxo-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetate, the crude title compound was prepared. Purification by ODS chromatography (5-60% CH₃CN/H₂O containing 0.1% TFA over 1 h), concentration and lyophilization gave the title compound: MS (ES) m/e 398.4 (M + H)⁺. Anal. Calcd for C₂₂H₂₇N₃O₄ · 1.5 CF₃CO₂H · 0.25 H₂O: C, 52.40; H, 5.10; N, 7.33. Found: C, 52.09; H, 5.26; N, 7.20.

Example 27

15 Preparation of (±)-2-benzyl-3-oxo-8-[3-(pyridin-2-ylamino)-1-propyloxy]-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetic acid

(a) Methyl (±)-2-benzyl-3-oxo-8-[3-[N-(1-oxopyridin-2-yl)-N-(*tert*-butoxycarbonyl)amino]-1-propyloxy]-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetate

20 According to the procedure of Example 24(a), except substituting benzyl bromide for the 4-trifluoromethylbenzyl bromide, the title compound (0.105 g, 20%) was prepared: MS (ES) m/e 590.4 (M + H)⁺.

(b) Methyl (±)-2-benzyl-3-oxo-8-[3-[N-(pyridin-2-yl)-N-(*tert*-butoxycarbonyl)amino]-1-propyloxy]-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetate

25 According to the procedure of Example 24(b), except substituting methyl (±)-2-benzyl-3-oxo-8-[3-[N-(1-oxopyridin-2-yl)-N-(*tert*-butoxycarbonyl)amino]-1-propyloxy]-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetate for the methyl (±)-3-oxo-8-[3-[N-(1-oxopyridin-2-yl)-N-(*tert*-butoxycarbonyl)amino]-1-propyloxy]-2-(4-trifluoromethylbenzyl)-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetate, the title compound (0.045 g, 44%) was prepared: MS (ES) m/e 574.4 (M + H)⁺.

(c) (±)-2-Benzyl-3-oxo-8-[3-[N-(pyridin-2-yl)-N-(*tert*-butoxycarbonyl)amino]-1-propyloxy]-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetic acid

35 According to the procedure of Example 1(c), except substituting methyl (±)-2-benzyl-3-oxo-8-[3-[N-(pyridin-2-yl)-N-(*tert*-butoxycarbonyl)amino]-1-propyloxy]-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetate for the ethyl (±)-8-[3-(2-pyridylamino)-1-

propyloxy]-3-oxo-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetate, the title compound (0.044 g, quantitative) was prepared: MS (ES) m/e 560.3 (M + H)⁺.

(d) (±)-2-Benzyl-3-oxo-8-[3-(pyridin-2-ylamino)-1-propyloxy]-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetic acid

According to the procedure of Example 25(a) except substituting (±)-2-benzyl-3-oxo-8-[3-[N-(pyridin-2-yl)-N-(*tert*-butoxycarbonyl)amino]-1-propyloxy]-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetic acid for the (±)-3-oxo-8-[3-[N-(pyridin-2-yl)-N-(*tert*-butoxycarbonyl)amino]-1-propyloxy]-2-(4-trifluoromethylbenzyl)-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetic acid, the title compound (0.014 g, 40%) was prepared: MS (ES) m/e 460.4 (M + H)⁺. Anal. Calcd for C₂₇H₂₉N₃O₄ · CF₃CO₂H · 2 H₂O: C, 57.14; H, 5.62; N, 6.89. Found: C, 57.44; H, 5.32; N, 6.87.

Example 28

15 Preparation of (±)-2-(carboxymethyl)-3-oxo-8-[3-(pyridin-2-ylamino)-1-propyloxy]-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetic acid

(a) Methyl (±)-2-(*tert*-butoxycarbonylmethyl)-3-oxo-8-[3-[N-(1-oxo-pyridin-2-yl)-N-(*tert*-butoxycarbonyl)amino]-1-propyloxy]-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetate

20 According to the procedure of Example 24(a) except substituting *tert*-butyl bromoacetate for the 4-trifluoromethylbenzyl bromide, the title compound (1.0g, 80%) was prepared: MS (ES) m/e 614.4 (M + H)⁺.

(b) Methyl (±)-2-(*tert*-butoxycarbonylmethyl)-3-oxo-8-[3-[N-(pyridin-2-yl)-N-(*tert*-butoxycarbonyl)amino]-1-propyloxy]-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetate

25 According to the procedure of Example 24(b) except substituting methyl (±)-2-(*tert*-butoxycarbonylmethyl)-3-oxo-8-[3-[N-(1-oxo-pyridin-2-yl)-N-(*tert*-butoxycarbonyl)amino]-1-propyloxy]-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetate for the methyl (±)-3-oxo-8-[3-[N-(1-oxopyridin-2-yl)-N-(*tert*-butoxycarbonyl)amino]-1-propyloxy]-2-(4-trifluoromethylbenzyl)-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetate, the title compound (0.72 g, 77%) was prepared: MS (ES) m/e 598.4 (M + H)⁺.

(c) Methyl (±)-2-(carboxymethyl)-3-oxo-8-[3-(pyridin-2-ylamino)-1-propyloxy]-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetate

35 According to the procedure of Example 25(a) except substituting methyl (±)-2-(*tert*-butoxycarbonylmethyl)-3-oxo-8-[3-[N-(pyridin-2-yl)-N-(*tert*-butoxycarbonyl)amino]-1-propyloxy]-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetate for the (±)-3-oxo-8-[3-[N-

(pyridin-2-yl)-N-(*tert*-butoxycarbonyl)amino]-1-propyloxy]-2-(4-trifluoromethylbenzyl)-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetic acid, the title compound (0.57 g, quantitative) was prepared: MS (ES) m/e 442.3 ($M + H$)⁺.

- 5 (d) (±)-2-(Carboxymethyl)-3-oxo-8-[3-(pyridin-2-ylamino)-1-propyloxy]-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetic acid

According to the procedure of Example 1(c) except substituting methyl (±)-2-(carboxymethyl)-3-oxo-8-[3-(pyridin-2-ylamino)-1-propyloxy]-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetate for the ethyl (±)-8-[3-(2-pyridylamino)-1-propyloxy]-3-oxo-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetate, the title compound (0.30 g, 56%) was prepared: MS (ES) m/e 428.4 ($M + H$)⁺. Anal. Calcd for $C_{22}H_{25}N_3O_6 \cdot 2 H_2O$: C, 57.01; H, 6.31; N, 9.07. Found: C, 57.27; H, 6.24; N, 8.86.

Example 29

15

Preparation of (±)-2-(4-aminobenzyl)-3-oxo-8-[3-(pyridin-2-ylamino)-1-propyloxy]-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetic acid

- 20 (a) Methyl(±)-2-(4-nitrobenzyl)-3-oxo-8-[3-[N-(1-oxo-pyridin-2-yl)-N-(*tert*-butoxycarbonyl)amino]-1-propyloxy]-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetate

According to the procedure of Example 24(a), except substituting 4-nitrobenzylbromide for the 4-trifluoromethylbenzyl bromide, the title compound (0.284 g, 69%) was prepared: MS (ES) m/e 635.3 ($M + H$)⁺.

- 25 (b) Methyl(±)-2-(4-aminobenzyl)-3-oxo-8-[3-[N-(1-oxo-pyridin-2-yl)-N-(*tert*-butoxycarbonyl)amino]-1-propyloxy]-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetate

According to the procedure of Example 24(b) except substituting methyl(±)-2-(4-nitrobenzyl)-3-oxo-8-[3-[N-(1-oxo-pyridin-2-yl)-N-(*tert*-butoxycarbonyl)amino]-1-propyloxy]-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetate for the methyl (±)-3-oxo-8-[3-[N-(1-oxopyridin-2-yl)-N-(*tert*-butoxycarbonyl)amino]-1-propyloxy]-2-(4-trifluoromethylbenzyl)-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetate, the title compound (0.104 g, 40%) was prepared: MS (ES) m/e 589.3 ($M + H$)⁺.

- 35 (c) (±)-2-(4-Aminobenzyl)-3-oxo-8-[3-[N-(pyridin-2-yl)-N-(*tert*-butoxycarbonyl)amino]-1-propyloxy]-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetic acid

According to the procedure of Example 1(c), except substituting methyl(±)-2-(4-aminobenzyl)-3-oxo-8-[3-[N-(1-oxo-pyridin-2-yl)-N-(*tert*-butoxycarbonyl)amino]-1-

propyloxy]-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetate for the ethyl (±)-8-[3-(2-pyridylamino)-1-propyloxy]-3-oxo-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetate. the title compound (0.08g, 79%) was prepared: MS (ES) m/e 575.4 (M + H)⁺.

- 5 (d) (±)-2-(4-Aminobenzyl)-3-oxo-8-[3-(pyridin-2-yl-amino)-1-propyloxy]-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetic acid

According to the procedure of Example 25(a) except substituting (±)-2-(4-aminobenzyl)-3-oxo-8-[3-[N-(pyridin-2-yl)-N-(*tert*-butoxycarbonyl)amino]-1-propyloxy]-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetic acid for the (±)-3-oxo-8-[3-[N-(pyridin-2-yl)-N-(*tert*-butoxycarbonyl)amino]-1-propyloxy]-2-(4-trifluoromethylbenzyl)-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetic acid, the title compound (0.029 g, 44%) was prepared: MS (ES) m/e 475.4 (M + H)⁺. Anal. Calcd for C₂₇H₃₀N₄O₄ · 2 CF₃CO₂H · 1.5 H₂O: C, 51.03; H, 4.83; N, 7.68. Found: C, 50.92; H, 4.78; N, 7.64.

15 Example 30

Preparation of (±)-3-oxo-8-[3-[N-(pyridin-2-yl)-N-(benzoyl)amino]-1-propyloxy]-2-(4-trifluoromethylbenzyl)-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetic acid

- 20 (a) Methyl (±)-3-oxo-8-[3-(1-oxo-pyridin-2-yl)amino]-1-propyloxy]-2-(4-trifluoromethylbenzyl)-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetate

According to the procedure of Example 25(a), except substituting methyl (±)-3-oxo-8-[3-[N-(1-oxopyridin-2-yl)-N-(*tert*-butoxycarbonyl)amino]-1-propyloxy]-2-(4-trifluoromethylbenzyl)-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetate for the (±)-3-oxo-8-[3-[N-(pyridin-2-yl)-N-(*tert*-butoxycarbonyl)amino]-1-propyloxy]-2-(4-trifluoromethylbenzyl)-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetic acid, the title compound (1.9 g, 90%) was prepared: MS (ES) m/e 558.3 (M + H)⁺.

- 30 (b) Methyl (±)-3-oxo-8-[3-(pyridin-2-yl)amino]-1-propyloxy]-2-(4-trifluoromethylbenzyl)-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetate

According to the procedure of Example 24(b), except substituting methyl (±)-3-oxo-8-[3-(1-oxo-pyridin-2-yl)amino]-1-propyloxy]-2-(4-trifluoromethylbenzyl)-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetate for the methyl (±)-3-oxo-8-[3-[N-(1-oxopyridin-2-yl)-N-(*tert*-butoxycarbonyl)amino]-1-propyloxy]-2-(4-trifluoromethylbenzyl)-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetate, the title compound (0.40 g, 88%) was prepared: MS (ES) m/e 542.3 (M + H)⁺.

(c) Methyl(±)-3-oxo-8-[3-[N-(pyridin-2-yl)-N-(benzoyl)amino]-1-propyloxy]-2-(4-trifluoromethylbenzyl)-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetate

Benzoyl chloride (0.094 mL, 0.8 mmol) was added dropwise to a solution of methyl (±)-3-oxo-8-[3-(pyridin-2-yl)amino]-1-propyloxy]-2-(4-trifluoromethylbenzyl)-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetate (0.4 g, 0.74 mmol) and diisopropylethylamine (0.5 mL, 2.9 mmol) in CH₂Cl₂ (10 mL). After 18 h, the solution was concentrated, and the residue was purified by silica gel chromatography (1:1 EtOAc/Hexane) to give the title compound (0.293 g, 61%): MS (ES) m/e 646.2 (M + H)⁺.

(d) (±)-3-Oxo-8-[3-[N-(pyridin-2-yl)-N-(benzoyl)amino]-1-propyloxy]-2-(4-trifluoromethylbenzyl)-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetic acid

According to the procedure of Example 1(c) except substituting methyl(±)-3-oxo-8-[3-[N-(pyridin-2-yl)-N-(benzoyl)amino]-1-propyloxy]-2-(4-trifluoromethylbenzyl)-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetate for the ethyl (±)-8-[3-(2-pyridylamino)-1-propyloxy]-3-oxo-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetate, the crude title compound was prepared. Purification by ODS chromatography (10-80% CH₃CN/H₂O containing 0.1% TFA over 1 h), concentration and lyophilization gave the title compound (0.025 g, 10%): MS (ES) m/e 632.4 (M + H)⁺. Anal. Calcd for C₃₅H₃₂F₃N₃O₅ · 0.85 CF₃CO₂H: C, 60.50; H, 4.54; N, 5.74. Found: C, 60.22; H, 4.35; N, 5.77.

Example 31

Preparation of (±)-3-oxo-8-[3-[N-(pyridin-2-yl)-N-(*tert*-butylacetyl)amino]-1-propyloxy]-2-(4-trifluoromethylbenzyl)-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetic acid

(a) Methyl (±)-3-oxo-8-[3-[N-(1-oxo-pyridin-2-yl)-N-(*tert*-butylacetyl)amino]-1-propyloxy]-2-(4-trifluoromethylbenzyl)-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetate

A solution of *tert*-butyl acetic acid (0.228 mL, 1.2 mmol) in CH₂Cl₂ (10 mL) was treated with oxalyl chloride (1 mL, 11.4 mmol), followed by DMF (0.0005 mL, 0.06 mmol). The reaction was stirred at RT for 1.5 h, then was concentrated. The residue was taken up in CH₂Cl₂ (5 mL) and was added dropwise to a solution of methyl (±)-3-oxo-8-[3-(1-oxo-pyridin-2-yl)amino]-1-propyloxy]-2-(4-trifluoromethylbenzyl)-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetate (0.35 g, 0.6 mmol) and Et₃N (0.5 mL, 2.4 mmol) in CH₂Cl₂ (10 mL). After 18 h the solution was washed sequentially with H₂O (1 x), 5% NaHCO₃ (2 x), H₂O (1 x), 5% citric acid (2 x), H₂O (1 x) and satd NaCl (1 x). The organic layer was concentrated to give the title compound (0.4 g, 97%): MS (ES) m/e 656.4 (M + H)⁺.

(b) Methyl (\pm)-3-oxo-8-[3-[N-(pyridin-2-yl)-N-(*tert*-butylacetyl)amino]-1-propyloxy]-2-(4-trifluoromethylbenzyl)-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetate

According to the procedure of Example 24(b), except substituting methyl (\pm)-3-oxo-8-[3-[N-(1-oxo-pyridin-2-yl)-N-(*tert*-butylacetyl)amino]-1-propyloxy]-2-(4-trifluoromethylbenzyl)-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetate for the methyl (\pm)-3-oxo-8-[3-[N-(1-oxopyridin-2-yl)-N-(*tert*-butoxycarbonyl)amino]-1-propyloxy]-2-(4-trifluoromethylbenzyl)-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetate, the title compound (0.22 g, 56%) was prepared: MS (ES) *m/e* 642.3 (M + H)⁺.

(c) (\pm)-3-Oxo-8-[3-[N-(pyridin-2-yl)-N-(*tert*-butylacetyl)amino]-1-propyloxy]-2-(4-trifluoromethylbenzyl)-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetic acid

According to the procedure of Example 1(c), except substituting methyl (\pm)-3-oxo-8-[3-[N-(pyridin-2-yl)-N-(*tert*-butylacetyl)amino]-1-propyloxy]-2-(4-trifluoromethylbenzyl)-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetate

for the ethyl (\pm)-8-[3-(2-pyridylamino)-1-propyloxy]-3-oxo-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetate, the crude title compound was prepared. Purification by ODS chromatography (10-80% CH₃CN/H₂O containing 0.1% TFA over 1 h), concentration and lyophilization gave the title compound (0.022 g, 10%): MS (ES) *m/e* 626.4 (M + H)⁺. Anal. Calcd for C₃₄H₃₈F₃N₃O₅ · 1 H₂O: C, 63.44; H, 6.26; N, 6.53. Found: C, 63.24; H, 5.96; N, 6.39.

Example 32

Preparation of (\pm)-3-Oxo-8-[3-[N-(pyridin-2-yl)-N-(isobutoxycarbonyl)amino]-1-propyloxy]-2-(4-trifluoromethylbenzyl)-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetic acid

(a) Methyl (\pm)-3-oxo-8-[3-[N-(1-oxo-pyridin-2-yl)-N-(isobutoxycarbonyl)amino]-1-propyloxy]-2-(4-trifluoromethylbenzyl)-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetate

According to the procedure of Example 30(c), except substituting isobutyl chloroformate for the benzoyl chloride, the title compound (0.47 g, 80%) was prepared: MS (ES) *m/e* 658.3 (M + H)⁺.

(b) Methyl (\pm)-3-oxo-8-[3-[N-(pyridin-2-yl)-N-(isobutoxycarbonyl)amino]-1-propyloxy]-2-(4-trifluoromethylbenzyl)-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetate

According to the procedure of Example 24(b), except substituting methyl(\pm)-3-oxo-8-[3-[N-(1-oxo-pyridin-2-yl)-N-(isobutoxycarbonyl)amino]-1-propyloxy]-2-(4-trifluoromethylbenzyl)-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetate for the methyl (\pm)-3-oxo-8-[3-[N-(1-oxopyridin-2-yl)-N-(*tert*-butoxycarbonyl)amino]-1-propyloxy]-2-(4-

trifluoromethylbenzyl)-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetate, the title compound (0.4 g, 63%) was prepared: MS (ES) m/e 642.3 (M + H)⁺.

(c) (±)-3-Oxo-8-[3-[N-(pyridin-2-yl)-N-(isobutoxycarbonyl)amino]-1-propyloxy]-2-(4-trifluoromethylbenzyl)-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetic acid

According to the procedure of Example 1(c), except substituting methyl(±)-3-oxo-8-[3-[N-(pyridin-2-yl)-N-(isobutoxycarbonyl)amino]-1-propyloxy]-2-(4-trifluoromethylbenzyl)-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetate for the ethyl (±)-8-[3-(2-pyridylamino)-1-propyloxy]-3-oxo-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetate, the crude title compound was prepared. Purification by ODS chromatography (10-80% CH₃CN/H₂O containing 0.1% TFA over 1 h), concentration and lyophilization gave the title compound (0.008g, 20%): MS (ES) m/e 628.3 (M + H)⁺. Anal Calcd. for C₃₃H₃₆F₃N₃O₆ · 0.25 CF₃CO₂H · 0.5 H₂O: C, 60.49; H, 5.64; N, 6.32. Found: C, 60.78; H, 5.50; N, 6.28.

Example 33

Preparation of (S)-3-oxo-8-[3-(pyridin-2-ylamino)-1-propyloxy]-2-(4-trifluoromethylbenzyl)-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetic acid

(a) Methyl (S)-3-oxo-8-[3-[N-(1-oxo-pyridin-2-yl)-N-(*tert*-butoxycarbonyl)amino]-1-propyloxy]-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetate

According to the procedure of Example 1(a), except substituting methyl (S)-8-hydroxy-3-oxo-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetate for the methyl (±)-8-hydroxy-3-oxo-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetate, the title compound (3.0 g, 83%) was prepared: MS (ES) m/e 500.3 (M + H)⁺.

(b) Methyl (S)-3-oxo-8-[3-[N-(1-oxo-pyridin-2-yl)-N-(*tert*-butoxycarbonyl)amino]-1-propyloxy]-2-(4-trifluoromethylbenzyl)-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetate

According to the procedure of Example 24(a), except substituting methyl (S)-3-oxo-8-[3-[N-(1-oxo-pyridin-2-yl)-N-(*tert*-butoxycarbonyl)amino]-1-propyloxy]-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetate for the methyl-(±)-3-oxo-8-[3-[N-(1-oxo-pyridin-2-yl)-N-(*tert*-butoxycarbonyl)amino]-1-propyloxy]-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetate, the title compound (2.3 g, 72%) was prepared: MS (ES) m/e 658.2 (M + H)⁺.

(c) Methyl (S)-3-oxo-8-[3-[N-(pyridin-2-yl)-N-(*tert*-butoxycarbonyl)amino]-1-propyloxy]-2-(4-trifluoromethylbenzyl)-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetate

According to the procedure of Example 24(b), except substituting methyl (S)-3-oxo-8-[3-[N-(1-oxo-pyridin-2-yl)-N-(*tert*-butoxycarbonyl)amino]-1-propyloxy]-2-(4-trifluoromethylbenzyl)-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetate for the methyl (±)-3-oxo-8-[3-[N-(1-oxopyridin-2-yl)-N-(*tert*-butoxycarbonyl)amino]-1-propyloxy]-2-(4-trifluoromethylbenzyl)-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetate, the title compound (1.1 g, 50%) was prepared: MS (ES) m/e 642.1 (M + H)⁺.

10 (d) (S)-3-oxo-8-[3-[N-(pyridin-2-yl)-N-(*tert*-butoxycarbonyl)amino]-1-propyloxy]-2-(4-trifluoromethylbenzyl)-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetic acid

According to the procedure of Example 24(c) except substituting methyl (S)-3-oxo-8-[3-[N-(pyridin-2-yl)-N-(*tert*-butoxycarbonyl)amino]-1-propyloxy]-2-(4-trifluoromethylbenzyl)-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetate for the methyl (±)-3-oxo-8-[3-[N-(pyridin-2-yl)-N-(*tert*-butoxycarbonyl)amino]-1-propyloxy]-2-(4-trifluoromethylbenzyl)-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetate, the title compound (0.8 g, 60%) was prepared: MS (ES) m/e 628.1 (M + H)⁺.

20 (e) (S)-3-Oxo-8-[3-(pyridin-2-yl-amino)-1-propyloxy]-2-(4-trifluoromethylbenzyl)-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetic acid

According to the procedure of Example 25(a) except substituting (S)-3-oxo-8-[3-[N-(pyridin-2-yl)-N-(*tert*-butoxycarbonyl)amino]-1-propyloxy]-2-(4-trifluoromethylbenzyl)-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetic acid for the (±)-3-oxo-8-[3-[N-(pyridin-2-yl)-N-(*tert*-butoxycarbonyl)amino]-1-propyloxy]-2-(4-trifluoromethylbenzyl)-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetic acid, the crude title compound was prepared. Purification by ODS chromatography (30% CH₃CN/H₂O containing 0.1% TFA over 1 h), concentration and lyophilization gave the title (0.657 g, 72%) compound: [α]_D^{-42°} (c 1.0, MeOH); MS (ES) m/e 528.1 (M + H)⁺. Anal. Calcd for C₂₈H₂₈F₃N₃O₄ · 2 CF₃CO₂H · 3.75 H₂O: C, 46.69; H, 4.59; N, 5.10. Found: C, 46.47; H, 4.58; N, 5.48.

Example 34Preparation of methyl (±)-3-oxo-8-[3-(pyridin-2-ylamino)-1-propyloxy]-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetate

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(a) Methyl (±)-3-oxo-8-[3-(pyridin-2-ylamino)-1-propyloxy]-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetate

According to the procedure of Example 1(b), except substituting isopropanol for the ethanol, the title compound (0.35 g, 76%) was prepared: MS (ES) m/e 384.4 (M + H)⁺.

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Example 35Preparation of (S)-3-oxo-8-[3-(1,4,5,6-tetrahydropyrimid-2-ylamino)-1-propyloxy]-2-[4-(trifluoromethyl)benzyl]-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetic acid

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a) Methyl (S)-8-[3-(4-nitrobenzyloxycarbonylamino)-1-propyloxy]-3-oxo-2-[4-(trifluoromethyl)benzyl]-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetate

To methyl (S)-8-hydroxy-3-oxo-2-[4-(trifluoromethyl)benzyl]-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetate (0.14 g, 0.34 mmol) and Ph₃P (0.13 g, 0.50 mmol) in CH₂Cl₂ (2 mL) at 0 °C was added dropwise a solution of 3-(4-nitrobenzyloxycarbonylamino)-1-propanol (0.13 g, 0.51 mmol) and diethylazodicarboxylate (0.08 mL, 0.50 mL). When the addition was complete, the ice bath was removed and the reaction was stirred at RT. After 18 h, the solvent was removed and the product was isolated by flash chromatography on silica gel (100% CHCl₃ to 5% MeOH/CHCl₃) to give the title compound (0.12 g) as a clear oil. ¹H NMR (400 MHz, CDCl₃) δ 8.18 (d, J = 8.2 Hz, 2H), 7.65 (m, 1H), 7.50 (m, 5H), 7.40 (d, J = 8.2 Hz, 1H), 7.03 (d, J = 9.8 Hz, 1H), 6.70 (m, 1H), 6.30 (s, 1H), 5.23 (m, 3H), 4.95 (d, J = 16.4 Hz, 1H), 4.50 (d, J = 16.4 Hz, 1H), 3.95 (m, 3H), 3.78 (s, 3H), 3.70 (m, 1H), 3.45 (m, 2H), 3.15 - 2.90 (m, 3H), 2.50 (dd, J = 19.2, 5.5 Hz, 1H), 1.95 (m, 2H).

30 b) Methyl (S)-8-(3-amino-1-propyloxy)-3-oxo-2-[4-(trifluoromethyl)benzyl]-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetate

To methyl (S)-8-[3-(4-nitrobenzyloxycarbonylamino)-1-propyloxy]-3-oxo-2-[4-(trifluoromethyl)benzyl]-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetate (0.12 g, 0.19 mmol) in MeOH (2 mL) was added 10% Pd/C (20 mg). The reaction vessel was flushed with hydrogen and then fitted with a hydrogen-filled balloon. After 4.5 h, the hydrogen was vented and the catalyst was removed by filtration through celite®. Removal of solvent

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gave the title compound (0.09 g) as a pale yellow residue. This material was used without further purification. MS (ES) m/e 465.3 ($M + H$)⁺.

- 5 c) Methyl (S)-3-oxo-8-[3-(pyrimidin-2-ylamino)-1-propyloxy]-2-[4-(trifluoromethyl)benzyl]-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetate

A solution of methyl (S)-8-(3-amino-1-propyloxy)-3-oxo-2-[4-(trifluoromethyl)benzyl]-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetate (0.09 g, 0.19 mmol), 2-bromopyrimidine (0.09 g, 0.57 mmol) and diisopropylethylamine (0.17 mL, 0.98 mmol) in DMF (2 mL) was heated at 80 °C for 18 h. The reaction was allowed to cool to
10 RT and was concentrated to give a yellow residue. Flash chromatography on silica gel (2% MeOH/EtOAc) gave the title compound (42 mg) as a clear oil. MS (ES) m/e 543.1 ($M + H$)⁺.

- 15 d) Methyl (S)-3-oxo-8-[3-(3,4,5,6-tetrahydropyrimid-2-ylamino)-1-propyloxy]-2-[4-(trifluoromethyl)benzyl]-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetate

A Parr hydrogenation apparatus was charged with methyl (S)-3-oxo-8-[3-(pyrimidin-2-ylamino)-1-propyloxy]-2-[4-(trifluoromethyl)benzyl]-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetate (42 mg, 0.08 mmol), glacial acetic acid (2 mL), concentrated HCl (0.2 mL), and 10% Pd/C (10 mg). The mixture was shaken under hydrogen (40 psi) for 5 h,
20 then the hydrogen was vented and the catalyst was removed by filtration through celite®. Evaporation of the solvents gave the crude title compound (52 mg) as a dark residue. This was used without further purification. MS (ES) m/e 547.2 ($M + H$)⁺.

- 25 e) (S)-3-Oxo-8-[3-(3,4,5,6-tetrahydropyrimid-2-ylamino)-1-propyloxy]-2-[4-(trifluoromethyl)benzyl]-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetic acid

To the crude methyl (S)-3-oxo-8-[3-(3,4,5,6-tetrahydropyrimid-2-ylamino)-1-propyloxy]-2-[4-(trifluoromethyl)benzyl]-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetate from Example 35d in EtOH (1 mL) was added 1 N NaOH (0.25 mL, 0.25 mmol). After stirring at RT for 8.5 h, the reaction was quenched by adding 1 N HCl (0.25 mL, 0.25 mmol). Removal of solvent gave a pale yellow solid. Preparative reverse phase HPLC (Hamilton PRP-1®, 30% CH₃CN/H₂O containing 0.1% TFA) gave the title compound
30 (18.1 mg) as a white powder. MS (ES) m/e 533.3 ($M + H$)⁺. Anal. Calcd for C₂₇H₃₁N₄F₃O₄ · 2 H₂O · 2 CF₃CO₂H: C, 46.74; H, 4.68; N, 7.03. Found: C, 46.34; H, 4.31; N, 6.82.

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Example 36Preparation of (±)-3-oxo-8-[3-(N-(pyridin-2-yl)-N-(methyl)amino)-1-propyloxy]-2-[4-(trifluoromethyl)benzyl]-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetic acid

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a) Methyl (±)-3-oxo-8-[3-[N-(1-oxopyridin-2-yl)-N-(methyl)amino]-1-propyloxy]-2-[4-(trifluoromethyl)benzyl]-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetic acid

According to the procedure of Example 25 (a), except substituting methyl (±)-3-oxo-8-[3-[N-(1-oxopyridin-2-yl)-N-(*tert*-butoxycarbonyl)amino]-1-propyloxy]-2-(4-trifluoromethylbenzyl)-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetate for the (±)-3-oxo-8-[3-[N-(pyridin-2-yl)-N-(*tert*-butoxycarbonyl)amino]-1-propyloxy]-2-(4-trifluoromethylbenzyl)-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetic acid, the HCl salt was prepared. This material was converted to the free base by partitioning between EtOAc and 5% NaHCO₃. The EtOAc layer was separated and concentrated to give the title compound
15 (4.1 g, 100%): MS (ES) m/e 558.3 (M + H)⁺.

b) Methyl(±)-3-oxo-8-[3-(N-(1-oxopyridin-2-yl)-N-methyl-amino)-1-propyloxy]-2-(4-trifluoromethylbenzyl)-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetate

According to the procedure of Example 26 (a), except substituting methyl (±)-3-oxo-8-[3-[N-(1-oxopyridin-2-yl)-N-(methyl)amino]-1-propyloxy]-2-[4-(trifluoromethyl)benzyl]-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetic acid for the methyl (±)-8-[3-[2-(N-oxopyridyl)amino]-1-propyloxy]-3-oxo-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetate, the title compound (3.0 g, 94%) was prepared: MS (ES) m/e 572.3 (M + H)⁺.

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c) Methyl(±)-3-oxo-8-[3-(N-(pyridin-2-yl)-N-(methyl)amino)-1-propyloxy]-2-(4-trifluoromethylbenzyl)-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetate

According to the procedure of Example 4 (b), except substituting methyl(±)-3-oxo-8-[3-(N-(1-oxopyridin-2-yl)-N-(methyl)amino)-1-propyloxy]-2-(4-trifluoromethylbenzyl)-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetate for the methyl (±)-8-[3-[2-(N-oxopyridyl)amino]-1-propyloxy]-2-methyl-3-oxo-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetate, the title compound (0.32 g, 60%) was prepared: MS (ES) m/e 556.2 (M + H)⁺.

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d) (±)-3-Oxo-8-[3-(N-(pyridin-2-yl)-N-(methyl)amino)-1-propyloxy]-2-[4-(trifluoromethyl)benzyl]-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetic acid

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According to the procedure of Example 4 (c), except substituting methyl(±)-3-oxo-8-[3-(N-(pyridin-2-yl)-N-(methyl)amino)-1-propyloxy]-2-(4-trifluoromethylbenzyl)-

2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetate for the methyl (±)-8-[3-(2-pyridylamino)-1-propyloxy]-2-methyl-3-oxo-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetate, the title compound (0.02 g, 15%) was prepared: MS (ES) m/e 542.1 (M + H)⁺. Anal. Calcd for C₂₉H₃₀N₃O₄F₃ · CF₃CO₂H · H₂O: C, 55.28; H, 4.94; N, 6.24. Found: C, 55.45; H, 4.68; N, 6.14.

Example 37

Preparation of (S)-3-oxo-8-[3-(pyridin-2-ylamino)-1-propyloxy]-2-(2,2,2-trifluoroethyl)-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetic acid

a) Methyl (S)-3-oxo-8-[3-(1-oxopyridin-2-ylamino)-1-propyloxy]-2-(2,2,2-trifluoroethyl)-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetate

To a stirred solution of methyl (S)-8-hydroxy-2-methyl-3-oxo-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetate (19 g, 57.4 mmol) in dry THF (400 mL) and dry DMF (200 mL) under argon were added 2-(3-hydroxypropylamino)pyridine N-oxide (11.6 g, 69 mmol) and triphenylphosphine (18.0 g, 69 mmol). After all solids had completely dissolved (~30 minutes), the reaction was cooled to 0 °C in an ice bath and diisopropyl azodicarboxylate (14.3 mL, 69 mmol) was added via syringe. The reaction was allowed to warm slowly to RT and was stirred for 18 h. Concentration and flash chromatography on silica gel (8:2:1 CHCl₃/EtOAc/EtOH) gave the title compound (20.83 g, 75%) as a solid foam. An additional 5.73 g of product can be obtained by recycling of the recovered starting material from the above reaction to give a total of 26.56 g (96%) of the title compound: MS (ES) m/e 482.2 (M + H)⁺; ¹H NMR (400 MHz, DMSO-d₆) δ 8.09 (dd, J = 6.5, 1.3 Hz, 1H), 7.29 (t, 1H), 7.18 (t, 1H), 7.02 (d, J = 9.2 Hz, 1H), 6.84-6.79 (m, 3H), 6.59 (t, 1H), 5.32 (d, J = 16.5 Hz, 1H), 4.28-4.14 (m, 2H), 4.16 (d, J = 16.5 Hz, 1H), 4.02 (t, 2H), 3.84 (m, 1H), 3.58 (s, 3H), 3.40 (dd, 2H), 3.01 (dd, 1H), 2.73 (dd, 1H), 2.70 (dd, 1H), 2.52 (dd, 1H), 2.02 (ddd, 2H).

b) Methyl (S)-3-oxo-8-[3-(pyridin-2-ylamino)-1-propyloxy]-2-(2,2,2-trifluoroethyl)-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetate

To a stirred solution of methyl (S)-3-oxo-8-[3-(1-oxopyridin-2-ylamino)-1-propyloxy]-2-(2,2,2-trifluoroethyl)-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetate (26.56 g, 55 mmol) in isopropanol (500 mL) were added 10% palladium on activated carbon (8 g, 7.5 mmol, carefully pre-wetted in isopropanol under Argon) and cyclohexene (55.7 mL, 550 mmol). The reaction was then heated to reflux under Argon in an oil bath set at 90 °C. After 6 h an additional amount of 10% palladium on activated carbon (8 g, 7.5 mmol,

carefully pre-wetted in isopropanol under Argon) and cyclohexene (55.7 mL, 550 mmol) were added. After an additional 18 h the reaction was hot-filtered through celite®, and the filter pad was washed with 1:1 MeOH/CHCl₃ (400 mL). The filtrate was concentrated under vacuum and the residue was purified by flash chromatography on silica gel (95:5 CHCl₃/MeOH) to give the title compound (19.50 g, 76%) as a white sticky foam: TLC (silica, 5% MeOH in CHCl₃) R_f 0.52; MS (ES) m/e 466.3 (M + H)⁺; ¹H NMR (400 MHz, DMSO-d₆) δ 7.94 (dd, 1H), 7.34 (t, 1H), 7.02 (d, J = 9.2 Hz, 1H), 6.81 (m, 2H), 6.54 (t, 1H), 6.46 (m, 2H), 5.31 (d, J = 16.5 Hz, 1H), 4.23-4.13 (m, 2H), 4.17 (d, J = 16.5 Hz, 1H), 4.02 (t, 2H), 3.82 (m, 1H), 3.58 (s, 3H), 3.36 (m, 2H), 3.01 (dd, 1H), 2.72 (dd, 1H), 2.68 (dd, 1H), 2.50 (dd, 1H), 1.96 (ddd, 2H).

c) (S)-3-Oxo-8-[3-(pyridin-2-ylamino)-1-propyloxy]-2-(2,2,2-trifluoroethyl)-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetic acid

To a stirred solution of methyl (S)-3-oxo-8-[3-(pyridin-2-ylamino)-1-propyloxy]-2-(2,2,2-trifluoroethyl)-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetate (19.50 g, 42 mmol) in dioxane (150 mL) was added aqueous 1 N NaOH (75 mL, 75 mmol). The cloudy reaction was stirred at RT for 2 h, then the resulting homogeneous solution was neutralized with aqueous 1 N HCl (75 mL, 75 mmol). The solution was concentrated to near dryness by rotary evaporation to precipitate out the product. The supernatant was decanted off and the remaining gummy solid was redissolved in methanol. The clear solution was then reconcentrated by rotary evaporation. The remaining solid was triturated with a small volume of water, filtered and dried under vacuum to give the title compound (16.38 g, 86%) as a white powder. HPLC (Hamilton PRP-1®, 25% CH₃CN/H₂O containing 0.1% TFA) k' = 3.1; [α]_D -112.3° (c, 1.0, MeOH); MS (ES) m/e 452.3 (M + H)⁺; ¹H NMR (400 MHz, DMSO-d₆) δ 7.95 (dd, 1H), 7.34 (dt, 1H), 7.02 (d, J = 9.2 Hz, 1H), 6.81 (m, 2H), 6.58 (t, 1H), 6.47 (m, 2H), 5.30 (d, J = 16.5 Hz, 1H), 4.27 - 4.13 (m, 2H), 4.15 (d, J = 16.5 Hz, 1H), 4.02 (t, 1H), 3.78 (m, 1H), 3.37 (m, 2H), 3.00 (dd, 1H), 2.69 (dd, 1H), 2.65 (dd, 1H), 2.41 (dd, 1H), 1.96 (ddd, 2H). Anal. Calcd for C₂₂H₂₄F₃N₃O₄: C, 58.53; H, 5.36; N, 9.31. Found: C, 58.37; H, 5.42; N, 9.20.

Example 38Preparation of (R)-3-oxo-8-[3-(pyridin-2-ylamino)-1-propyloxy]-2-(2,2,2-trifluoroethyl)-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetic acid

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a) Methyl (R)-3-oxo-8-[3-(1-oxopyridin-2-ylamino)-1-propyloxy]-2-(2,2,2-trifluoroethyl)-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetate

A solution of 2-[(3-hydroxy-1-propyl)amino]pyridine-N-oxide (0.33 g, 2 mmole) and diethyl azodicarboxylate (0.3 mL, 2 mmole) in anhydrous DMF (10 mL) was added slowly dropwise to a solution of methyl (R)-8-hydroxy-3-oxo-2-(2,2,2-trifluoroethyl)-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetate (0.3 g, 1 mmole) and triphenylphosphine (0.485g, 26 mmole) in anhydrous CH₂Cl₂ (10 mL) at RT. After 17 hr, the reaction was concentrated. Silica gel chromatography (gradient: 0.5%- 5% MeOH/CH₂Cl₂) gave the title compound (0.35 g, 80%) as a colorless oil: MS (ES) m/e 482.3 (M + H)⁺.

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b) Methyl (R)-3-oxo-8-[3-(pyridin-2-ylamino)-1-propyloxy]-2-(2,2,2-trifluoroethyl)-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetate

A mixture of methyl (R)-3-oxo-8-[3-(1-oxopyridin-2-ylamino)-1-propyloxy]-2-(2,2,2-trifluoroethyl)-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetate (0.35 g, 0.7 mmole), cyclohexene (0.75 mL, 7 mmole), 10% Pd/C (88 mg, 0.07 mmole), and isopropanol (9 mL) was heated to reflux under argon. After 18 hr, additional 10% Pd/C (36 mg, 0.03 mmole) and cyclohexene (0.75 mL, 7 mmole) were added. After 36 hr, the reaction was hot-filtered through celite®, and the filter pad was washed with hot EtOAc. Concentration left a yellow oil. Silica gel chromatography (1%-5% MeOH in CH₂Cl₂) gave the title compound (0.26 g, 77%) as a colorless oil: MS (ES) m/e 466.2 (M + H)⁺.

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c) (R)-3-Oxo-8-[3-(pyridin-2-ylamino)-1-propyloxy]-2-(2,2,2-trifluoroethyl)-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetic acid

LiOH · H₂O (25 mg, 0.6 mmole) was added to a solution of methyl (R)-8-[3-(2-pyridylamino)-1-propyloxy]-3-oxo-2-(2,2,2-trifluoroethyl)-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetate (0.25 g, 0.54 mmole) in THF (5 mL) and H₂O (2 mL) at RT. After 18 hr, the reaction was concentrated to dryness and the residue was dissolved in H₂O (4 mL). The solution was carefully brought to pH ≈ 4 with 3.0 N HCl. The precipitate was collected and dried in high vacuum at 40 - 45 °C to afford the title compound (0.15 g, 62%) as an off-white solid: MS (ES) m/e 452.1 (M + H)⁺. Anal. Calcd for C₂₂H₂₄F₃N₃O₄ · 0.5 H₂O: C, 57.38; H, 5.47; N, 9.12. Found: C, 57.72; H, 5.24; N, 8.92.

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Example 39Preparation of (S)-8-[3-(4-methylpyridin-2-ylamino)-1-propyloxy]-3-oxo-2-(2,2,2-trifluoroethyl)-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetic acid

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a) Methyl (S)-8-[3-(4-methyl-1-oxopyridin-2-ylamino)-1-propyloxy]-3-oxo-2-(2,2,2-trifluoroethyl)-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetate

A solution of 2-[(3-hydroxy-1-propyl)amino]-4-methylpyridine-N-oxide (0.60 g, 3.6 mmole) and diethyl azodicarboxylate (0.6 mL, 3.6 mmole) in anhydrous CH_2Cl_2 (12 mL) was added dropwise over 3-4 min to a solution of methyl (S)-8-hydroxy-3-oxo-2-(2,2,2-trifluoroethyl)-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetate (0.60g, 1.8 mmole) and triphenylphosphine (0.95g, 3.6 mmole) in anhydrous CH_2Cl_2 (6 mL) at RT. After 17 hr, the reaction was concentrated. Silica gel chromatography (gradient: 1%- 5% MeOH/ CH_2Cl_2) gave the title compound (0.45g, 49%) as an off-white foam: MS (ES) m/e 496.3 (M + H)⁺.

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b) Methyl (S)-8-[3-(4-methylpyridin-2-ylamino)-1-propyloxy]-3-oxo-2-(2,2,2-trifluoroethyl)-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetate

A mixture of methyl (S)-8-[3-(4-methyl-1-oxopyridin-2-ylamino)-1-propyloxy]-3-oxo-2-(2,2,2-trifluoroethyl)-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetate (0.45 g, 0.9 mmole), cyclohexene (0.93 mL, 9 mmole), 10% Pd/C (0.2 g, 0.18 mmole), and isopropanol (9 mL) was heated to reflux under argon. After 18 hr, additional 10% Pd/C (0.2 g, 0.18 mmole) and cyclohexene (0.27 mL, 2.65 mmole) were added. After 36 hr, the reaction was hot-filtered through celite®, and the filter pad was washed with hot EtOAc. Concentration left a yellow oil. Silica gel chromatography (1%-3% MeOH in CH_2Cl_2) gave the title compound (0.32g, 74%) as a white foam: MS (ES) m/e 480.2 (M + H)⁺.

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c) (S)-8-[3-(4-Methylpyridin-2-ylamino)-1-propyloxy]-3-oxo-2-(2,2,2-trifluoroethyl)-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetic acid

LiOH · H₂O (33 mg, 0.79 mmole) was added to a solution of methyl (S)-8-[3-(4-methylpyridin-2-ylamino)-1-propyloxy]-3-oxo-2-(2,2,2-trifluoroethyl)-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetate (0.32 g, 0.67 mmole) in THF (5 mL) and H₂O (2 mL) at RT. After 18 hr, the reaction was concentrated to dryness and the residue was dissolved in H₂O (4 mL). The solution was extracted with ethyl acetate, then was carefully brought to pH ≈ 5 with 3.0 N HCl. The precipitate was collected and dried in high vacuum at 40 - 45 °C to afford the title compound (0.22 g, 71%) as an off-white solid: MS (ES) m/e 466.1 (M +

35

H)⁺. Anal. Calcd for C₂₃H₂₆F₃N₃O₄: C, 59.35; H, 5.63; N, 9.03. Found: C, 58.97; H, 5.55; N, 8.73.

Example 40

5

Preparation of (S)-8-[2-[6-(methylamino)pyridin-2-yl]-1-ethoxy]-3-oxo-2-(2,2,2-trifluoroethyl)-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetic acid

- 10 a) Methyl (S)-8-[2-[6-(methylamino)pyridin-2-yl]-1-ethoxy]-3-oxo-2-(2,2,2-trifluoroethyl)-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetate

According to the method of Example 37(a), except substituting 6-(methylamino)-2-pyridylethanol for the 2-[(3-hydroxy-1-propyl)amino]pyridine-N-oxide, and substituting (S)-8-hydroxy-3-oxo-2-(2,2,2-trifluoroethyl)-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetate for the (R)-8-hydroxy-3-oxo-2-(2,2,2-trifluoroethyl)-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetate, the title compound was prepared as a colorless oil: MS (ES) m/e 466.2 (M + H)⁺.

- 20 b) (S)-8-[2-[6-(Methylamino)pyridin-2-yl]-1-ethoxy]-3-oxo-2-(2,2,2-trifluoroethyl)-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetic acid

According to the method of Example 37(c), except substituting methyl (S)-8-[2-[6-(methylamino)pyridin-2-yl]-1-ethoxy]-3-oxo-2-(2,2,2-trifluoroethyl)-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetate for the methyl (R)-8-[3-(2-pyridylamino)-1-propyloxy]-3-oxo-2-(2,2,2-trifluoroethyl)-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetate, the title compound was prepared as a white solid: MS (ES) m/e 452.2 (M + H)⁺. Anal. Calcd for C₂₂H₂₄F₃N₃O₄ · 0.7 H₂O: C, 56.94; H, 5.52; N, 9.05. Found: C, 56.80; H, 5.19; N, 8.85.

Example 41

- 30 Preparation of (S)-3-oxo-8-[3-(pyridin-2-ylamino)-1-propyloxy]-2-(2-phenylethyl)-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetic acid

- a) Methyl (S)-3-oxo-8-[3-(1-oxopyridin-2-ylamino)-1-propyloxy]-2-(2-phenylethyl)-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetate

35 A solution of 2-[(3-hydroxy-1-propyl)amino]pyridine-N-oxide (336 mg, 2.0 mmole) and diethyl azodicarboxylate (0.3 mL, 2.0 mmole) in anhydrous DMF (10 mL) was added to a solution of methyl (S)-8-hydroxy-3-oxo-2-(2-phenylethyl)-2,3,4,5-tetrahydro-

1H-2-benzazepine-4-acetate (350 mg, 1.0 mmole) and triphenylphosphine (525 mg, 2.0 mmole) in anhydrous DMF (10 mL) at RT. After 24 hr the mixture was concentrated. Flash silica gel chromatography (gradient: EtOAc (500 mL) then 5% MeOH/CHCl₃) gave the title compound as an orange foam (288 mg, 57%): MS (ES) m/e 504 (M + H)⁺.

5

b) Methyl (S)-3-oxo-8-[3-(pyridin-2-ylamino)-1-propyloxy]-2-(2-phenylethyl)-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetate

A mixture of methyl (S)-3-oxo-8-[3-(1-oxopyridin-2-ylamino)-1-propyloxy]-2-(2-phenylethyl)-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetate (288 mg, 0.57 mmole),
10 cyclohexene (0.6 mL, 5.8 mmole), 10% Pd/C (62 mg, 0.58 mmole), and 2-propanol (6 mL) was heated to reflux under argon. After 31 hr the mixture was hot filtered through a pad of celite®, the filter pad was washed with hot 1:1 MeOH/CHCl₃ (200 mL), and the filtrate was concentrated. Flash silica gel chromatography (5% MeOH/CHCl₃) followed by a second flash silica gel chromatography (50% THF/cyclohexane) gave the title compound as
15 an off-white foam (133 mg, 48%): MS (ES) m/e 488 (M + H)⁺.

c) (S)-3-Oxo-8-[3-(pyridin-2-ylamino)-1-propyloxy]-2-(2-phenylethyl)-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetic acid

1.0 N LiOH (0.3 mL, 0.3 mmole) was added to a solution of methyl (S)-3-oxo-8-[3-(pyridin-2-ylamino)-1-propyloxy]-2-(2-phenylethyl)-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetate (133 mg, 0.27 mmole) in THF (1.5 mL) and H₂O (1.2 mL) at 0 °C. The mixture was allowed to warm to RT over 18 hr. The mixture was washed with Et₂O (2 x 5 mL) then a mild vacuum was applied to remove residual organic solvents. The aqueous layer was passed through a 0.45 µm Acrodisk filter, then was carefully acidified to pH 6 using
25 10% HCl in H₂O at 0 °C. The precipitate was collected, washed with H₂O, and dried under vacuum at 50 °C to give the title compound as a white solid (62 mg, 48%): MS (ES) m/e 474 (M + H)⁺. Anal. Calcd for C₂₈H₃₁N₃O₄ · 0.75 H₂O: C, 69.05; H, 6.75; N, 8.63. Found: C, 69.05; H, 6.66; N, 8.55.

Example 42Preparation of (S)-8-[2-[6-(methylamino)pyridin-2-yl]ethoxy]-3-oxo-2-(2-phenylethyl)-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetic acid

5

a) Methyl (S)-8-[2-[6-(methylamino)pyridin-2-yl]ethoxy]-3-oxo-2-(2-phenylethyl)-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetate

Diisopropyl azodicarboxylate (0.3 mL, 1.5 mmole) was added to a solution of (S)-8-hydroxy-3-oxo-2-(2-phenylethyl)-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetate (350 mg, 1.0 mmole), 6-(methylamino)-2-pyridylethanol (228 mg, 1.5 mmole), and triphenylphosphine (393 mg, 1.5 mmole) in anhydrous THF (10 mL) at 0 °C. The mixture was allowed to warm to RT over 72 hr then was concentrated. Flash silica gel chromatography (50% EtOAc/hexanes) followed by a second flash silica gel chromatography (25% EtOAc/hexanes) gave the title compound as a white foam (250 mg, 51%): MS (ES) m/e 488 (M + H)⁺.

10
15

b) (S)-8-[2-[6-(Methylamino)pyridin-2-yl]ethoxy]-3-oxo-2-(2-phenylethyl)-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetic acid

1.0N LiOH (0.62 mL, 0.62 mmole) was added to a solution of methyl (S)-8-[2-[6-(methylamino)pyridin-2-yl]ethoxy]-3-oxo-2-(2-phenylethyl)-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetate (250 mg, 0.51 mmole) in THF (2.5 mL) and H₂O (1.9 mL) at 0 °C, and the reaction was allowed to stir at RT for 18 hr. The mixture was washed with Et₂O (2 x 5 mL) then a mild vacuum was applied to remove residual organic solvents. The aqueous layer was passed through a 0.45 µm Acrodisk filter then was carefully acidified to pH 6 using 10% HCl in H₂O at 0 °C. The precipitate was collected, washed with H₂O, and dried under vacuum at 50 °C to give the title compound (134 mg, 55%) as a white solid: MS (ES) m/e 474 (M + H)⁺. Anal. Calcd for C₂₈H₃₁N₃O₄ · 0.75 H₂O: C, 69.05; H, 6.73; N, 8.63. Found: C, 69.23; H, 6.59; N, 8.55.

20
25

Example 43Preparation of (S)-8-[2-[6-(methylamino)pyridin-2-yl]-1-ethoxy]-3-oxo-2-[4-(trifluoromethyl)benzyl]-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetic acid

5

a) Methyl (S)-8-[2-[6-(methylamino)pyridin-2-yl]-1-ethoxy]-3-oxo-2-[4-(trifluoromethyl)benzyl]-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetate

To a solution of methyl (S)-8-hydroxy-3-oxo-2-[4-(trifluoromethyl)benzyl]-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetate (0.18 g, 0.44 mmol) and Ph_3P (0.23 g, 0.88 mmol) in CH_2Cl_2 (2 mL) was added a solution of 6-(methylamino)-2-pyridylethanol (0.13 g, 0.88 mmol) and diethylazodicarboxylate (0.14 mL, 0.89 mmol) in CH_2Cl_2 (2 mL). After 2 days at RT, the solvent was removed under reduced pressure. Radial chromatography on silica gel (6 mm plate, 5% MeOH/ CHCl_3) gave a clear oil (0.63 g) which contained a mixture of the title compound together with unreacted methyl (S)-8-hydroxy-3-oxo-2-[4-(trifluoromethyl)benzyl]-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetate. This material was further purified by radial chromatography on silica gel (6 mm plate, 50% EtOAc/hexanes) to give the title compound (0.12 g) as a clear oil: MS (ES) m/e 542.3 ($\text{M} + \text{H}$)⁺.

b) (S)-8-[2-[6-(Methylamino)pyridin-2-yl]-1-ethoxy]-3-oxo-2-[4-(trifluoromethyl)benzyl]-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetic acid

To a solution of methyl (S)-8-[2-[6-(methylamino)pyridin-2-yl]-1-ethoxy]-3-oxo-2-[4-(trifluoromethyl)benzyl]-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetate (0.12 g, 0.22 mmol) in EtOH (2 mL) was added 1 N NaOH (0.50 mL). After 3.5 h at RT, the bulk of the solvent was removed under reduced pressure to give a white residue. This was dissolved in water and the solution was neutralized to pH = 7 with 1 N HCl. The resulting precipitate was collected and dried under vacuum to give the title compound (28.1 mg) as a white solid: $[\alpha]_D -74.0^\circ$ (c 0.05, EtOH); MS (ES) m/e 528.3 ($\text{M} + \text{H}$)⁺. Anal. Calcd for $\text{C}_{28}\text{H}_{28}\text{F}_3\text{N}_3\text{O}_4 \cdot 0.5 \text{H}_2\text{O}$: C, 62.68; H, 5.45; N, 7.83. Found: C, 62.60; H, 5.35; N, 7.66.

30

Example 44Parenteral Dosage Unit Composition

35 A preparation which contains 20 mg of the compound of Example 1 as a sterile dry powder is prepared as follows: 20 mg of the compound is dissolved in 15 mL of distilled water. The solution is filtered under sterile conditions into a 25 mL multi-dose ampoule

and lyophilized. The powder is reconstituted by addition of 20 mL of 5% dextrose in water (D5W) for intravenous or intramuscular injection. The dosage is thereby determined by the injection volume. Subsequent dilution may be made by addition of a metered volume of this dosage unit to another volume of D5W for injection, or a metered dose may be added to another mechanism for dispensing the drug, as in a bottle or bag for IV drip infusion or other injection-infusion system.

Example 45

Oral Dosage Unit Composition

A capsule for oral administration is prepared by mixing and milling 50 mg of the compound of Example 1 with 75 mg of lactose and 5 mg of magnesium stearate. The resulting powder is screened and filled into a hard gelatin capsule.

Example 46

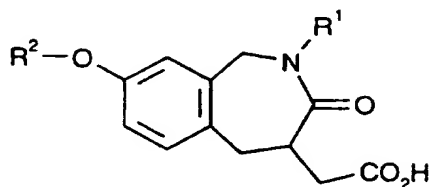
Oral Dosage Unit Composition

A tablet for oral administration is prepared by mixing and granulating 20 mg of sucrose, 150 mg of calcium sulfate dihydrate and 50 mg of the compound of Example 1 with a 10% gelatin solution. The wet granules are screened, dried, mixed with 10 mg starch, 5 mg talc and 3 mg stearic acid; and compressed into a tablet.

The above description fully discloses how to make and use the present invention. However, the present invention is not limited to the particular embodiments described hereinabove, but includes all modifications thereof within the scope of the following claims. The various references to journals, patents and other publications which are cited herein comprises the state of the art and are incorporated herein by reference as though fully set forth.

What is claimed is:

1. A compound according to formula (I):



(I)

wherein:

R^1 is R^7 , or A-C₀₋₄alkyl, A-C₂₋₄alkenyl, A-C₂₋₄alkynyl, A-C₃₋₄oxoalkenyl, A-C₃₋₄oxoalkynyl, A-C₁₋₄aminoalkyl, A-C₃₋₄aminoalkenyl, A-C₃₋₄aminoalkynyl, optionally substituted by any accessible combination of one or more of R^{10} or R^7 ;

A is H, C₃₋₆cycloalkyl, Het or Ar;

R^7 is -COR⁸, -COCR'₂R⁹, -C(S)R⁸, -S(O)_mOR', -S(O)_mNR'R'', -PO(OR'), -PO(OR')₂, -NO₂, or tetrazolyl;

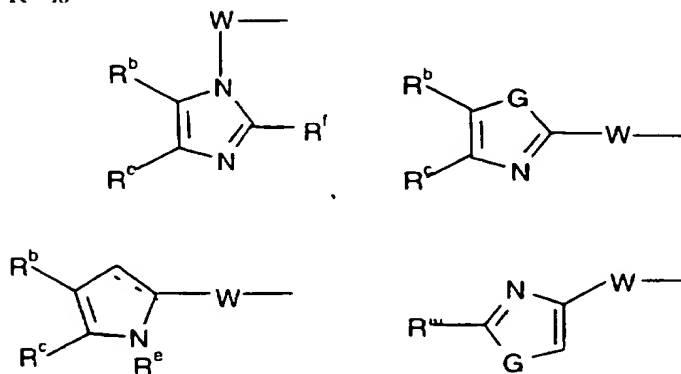
each R⁸ independently is -OR', -NR'R'', -NR'SO₂R', -NR'OR', or -OCR'₂CO(O)R';

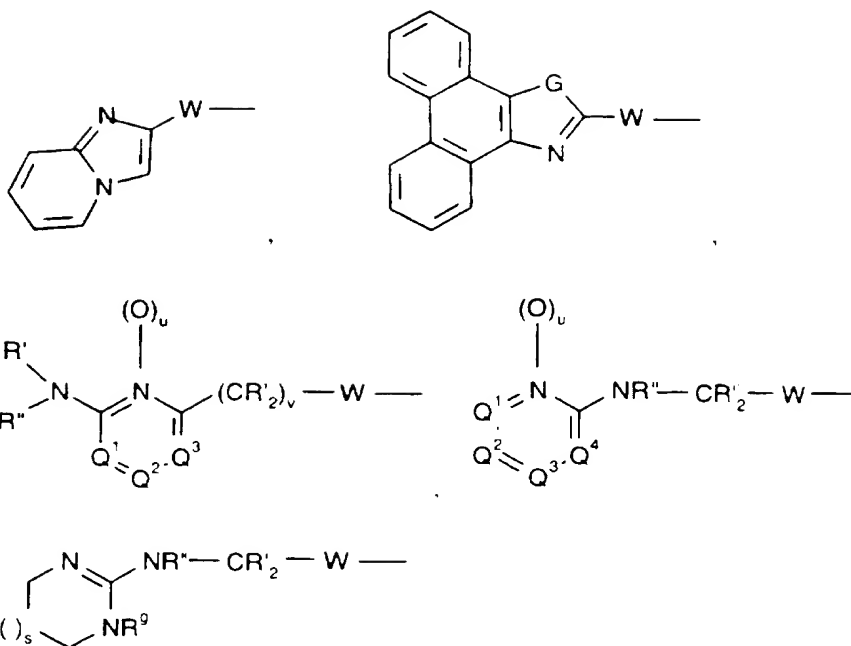
R^9 is -OR', -CN, -S(O)_rR', -S(O)_mNR'₂, -C(O)R', C(O)NR'₂, or -CO₂R';

R^{10} is H, halo, -OR¹¹, -CN, -NR'R¹¹, -NO₂, -CF₃, CF₃S(O)_r, -CO₂R', -CONR'₂, A-C₀₋₆alkyl-, A-C₁₋₆oxoalkyl-, A-C₂₋₆alkenyl-, A-C₂₋₆alkynyl-, A-C₀₋₆alkyloxy-, A-C₀₋₆alkylamino- or A-C₀₋₆alkyl-S(O)_r-;

R^{11} is R', -C(O)R', -C(O)NR'₂, -C(O)OR', -S(O)_mR', or -S(O)_mNR'₂;

R^2 is





5

W is $-(\text{CHR}^g)_a\text{-U-}(\text{CHR}^g)_b\text{-}$;

U is absent or CO, CR^gE_2 , $\text{C(=CR}^g\text{E}_2)$, S(O)_k , O, NR^g , CR^gOR^g , $\text{CR}^g(\text{OR}^k)\text{CR}^g\text{E}_2$, $\text{CR}^g\text{E}_2\text{CR}^g(\text{OR}^k)$, $\text{C(O)CR}^g\text{E}_2$, $\text{CR}^g\text{E}_2\text{C(O)}$, CONR^i , NR^iCO , OC(O) , C(O)O , C(S)O , OC(S) ,
 10 C(S)NR^g , $\text{NR}^g\text{C(S)}$, $\text{S(O)}_2\text{NR}^g$, $\text{NR}^g\text{S(O)}_2$, N=N , NR^gNR^g , $\text{NR}^g\text{CR}^g\text{E}_2$, $\text{CR}^g\text{E}_2\text{NR}^g$, $\text{CR}^g\text{E}_2\text{O}$, OCR^gE_2 , $\text{C}\equiv\text{C}$ or $\text{CR}^g=\text{CR}^g$;

G is NR^e , S or O;

R^g is H, $\text{C}_{1-6}\text{alkyl}$, $\text{Het-C}_{0-6}\text{alkyl}$, $\text{C}_{3-7}\text{cycloalkyl-C}_{0-6}\text{alkyl}$ or $\text{Ar-C}_{0-6}\text{alkyl}$;

R^k is R^g , $-\text{C(O)R}^g$, or $-\text{C(O)OR}^f$;

15 R^i is H, $\text{C}_{1-6}\text{alkyl}$, $\text{Het-C}_{0-6}\text{alkyl}$, $\text{C}_{3-7}\text{cycloalkyl-C}_{0-6}\text{alkyl}$, $\text{Ar-C}_{0-6}\text{alkyl}$, or $\text{C}_{1-6}\text{alkyl}$ substituted by one to three groups chosen from halogen, CN, NR^gE_2 , OR^g , SR^g , CO_2R^g , and $\text{CON(R}^g)_2$;

R^f is H, $\text{C}_{1-6}\text{alkyl}$ or $\text{Ar-C}_{0-6}\text{alkyl}$;

20 R^e is H, $\text{C}_{1-6}\text{alkyl}$, $\text{Ar-C}_{0-6}\text{alkyl}$, $\text{Het-C}_{0-6}\text{alkyl}$, $\text{C}_{3-7}\text{cycloalkyl-C}_{0-6}\text{alkyl}$, or $(\text{CH}_2)_k\text{CO}_2\text{R}^g$;

R^b and R^c are independently selected from H, $\text{C}_{1-6}\text{alkyl}$, $\text{Ar-C}_{0-6}\text{alkyl}$, $\text{Het-C}_{0-6}\text{alkyl}$, or $\text{C}_{3-6}\text{cycloalkyl-C}_{0-6}\text{alkyl}$, halogen, CF_3 , OR^f , $\text{S(O)}_k\text{R}^f$, COR^f , NO_2 , $\text{N(R}^f)_2$, $\text{CO(NR}^f)_2$, $\text{CH}_2\text{N(R}^f)_2$, or R^b and R^c are joined together to form a five or six membered aromatic or non-aromatic carbocyclic or heterocyclic ring, optionally substituted by up to
 25 three substituents chosen from halogen, CF_3 , $\text{C}_{1-4}\text{alkyl}$, OR^f , $\text{S(O)}_k\text{R}^f$, COR^f , CO_2R^f , OH, NO_2 , $\text{N(R}^f)_2$, $\text{CO(NR}^f)_2$, and $\text{CH}_2\text{N(R}^f)_2$; or methylenedioxy;

Q^1 , Q^2 , Q^3 and Q^4 are independently N or C- R^y , provided that no more than one of Q^1 , Q^2 , Q^3 and Q^4 is N;

R' is H, C_{1-6} alkyl, Ar- C_{0-6} alkyl or C_{3-6} cycloalkyl- C_{0-6} alkyl;

R'' is R' , -C(O) R' or -C(O)OR';

5 R''' is H, C_{1-6} alkyl, Ar- C_{0-6} alkyl, Het- C_{0-6} alkyl, or C_{3-6} cycloalkyl- C_{0-6} alkyl, halogen, CF_3 , OR^f , $S(O)_kR^f$, COR^f , NO_2 , $N(R^f)_2$, $CO(NR^f)_2$, $CH_2N(R^f)_2$;

R^y is H, halo, -OR g , -SR g , -CN, -NR $^gR^k$, -NO $_2$, -CF $_3$, $CF_3S(O)_r$ -, -CO $_2R^g$, -COR g or -CONR g_2 , or C_{1-6} alkyl optionally substituted by halo, -OR g , -SR g , -CN, -NR $^gR''$, -NO $_2$, -CF $_3$, $R'S(O)_r$ -, -CO $_2R^g$, -COR g or -CONR g_2 ;

10 a is 0, 1 or 2;

b is 0, 1 or 2;

k is 0, 1 or 2;

m is 1 or 2;

r is 0, 1 or 2;

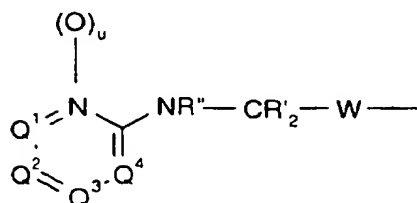
15 s is 0, 1 or 2;

u is 0 or 1; and

v is 0 or 1;

or a pharmaceutically acceptable salt thereof.

20 2. A compound according to claim 1 in which R^2 is

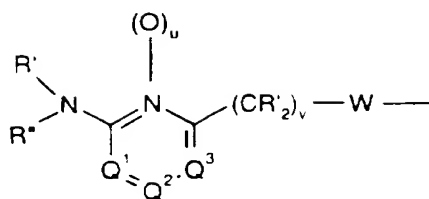


,wherein Q^1 , Q^2 , and Q^3 are each C- R^y , Q^4 is

C- R^y or N and u is 0.

25 3. A compound according to claim 2 in which each R' is H, R'' is H, C_{1-6} alkyl, -C(O) C_{1-6} alkyl, C(O)OC $_{1-6}$ alkyl, -C(O) C_{0-6} alkyl-Ar, or C(O)OC $_{0-6}$ alkyl-Ar, W is -CH $_2$ -CH $_2$ -, and R^y is H, halo, -OR g , -SR g , -CN, -NR $^gR^k$, -NO $_2$, -CF $_3$, $CF_3S(O)_r$ -, -CO $_2R^g$, -COR g -CONR g_2 , or C_{1-6} alkyl.

30 4. A compound according to claim 1 in which R^2 is



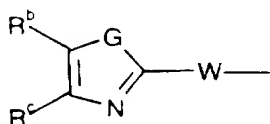
, wherein Q^1 , Q^2 , and Q^3 are each CH and u is

0.

5. A compound according to claim 4 in which each R' is H, R'' is H or

5 C_{1-4} alkyl, v is 0 and W is $-CH_2-CH_2-$.

6. A compound according to claim 1 in which R^2 is

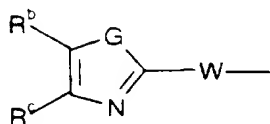


, wherein G is NH and R^b and R^c are each H.

10

7. A compound according to claim 6 in which W is $-NR^E-(CHR^E)_b-$.

8. A compound according to claim 1 in which R^2 is



15

, wherein G is NH and R^b and R^c are joined together to form a five or six membered aromatic or non-aromatic carbocyclic or heterocyclic ring, optionally substituted by up to three substituents chosen from halogen, CF_3 , C_{1-4} alkyl, OR^f , $S(O)_kR^f$, COR^f , CO_2R^f , OH, NO_2 , $N(R^f)_2$, $CO(NR^f)_2$, and $CH_2N(R^f)_2$; or methylenedioxy.

20

9. A compound according to claim 8 in which R^b and R^c are joined together to form a six membered aromatic carbocyclic ring.

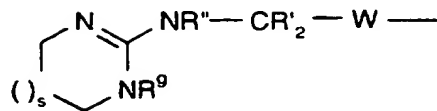
10. A compound according to claim 9 in which W is $-CH_2-CH_2-$.

25

11. A compound according to claim 8 in which R^b and R^c are joined together to form a six membered aromatic heterocyclic ring.

12. A compound according to claim 11 in which W is $-CH_2-CH_2-$.

13. A compound according to claim 1 in which R² is



, wherein each R' is H, R'' is H or C₁₋₄alkyl,

5 R⁸ is H or C₁₋₄alkyl and s is 0, 1 or 2.

14. A compound according to claim 13 in which W is -CH₂-CH₂-.

15. A compound according to claim 1 in which R¹ is H, C₁₋₆alkyl,
10 Ar-C₀₋₆alkyl, Het-C₀₋₆alkyl, C₃₋₆cycloalkyl-C₀₋₆alkyl, -CH₂CF₃, -(CH₂)₁₋₂C(O)OR', or
-(CH₂)₂OR', in which R' is H or C₁₋₄alkyl.

16. A compound according to claim 15 in which R¹ is H, C₁₋₄alkyl,
15 Ph-C₀₋₄alkyl, -CH₂CF₃, -(CH₂)₁₋₂C(O)OR', or -(CH₂)₂OR', in which R' is H or C₁₋₄alkyl.

17. A compound according to claim 16 in which R¹ is -CH₂CF₃.

18. A compound according to claim 1 which is:

- 20 (±)-8-[3-(2-pyridylamino)-1-propyloxy]-3-oxo-2,3,4,5-tetrahydro-1H-2-
benzazepine-4-acetic acid;
(±)-8-[3-(4-amino-2-pyridylamino)-1-propyloxy]-3-oxo-2,3,4,5-tetrahydro-1H-2-
benzazepine-4-acetic acid;
(±)-8-[3-(4-methoxy-2-pyridylamino)-1-propyloxy]-3-oxo-2,3,4,5-tetrahydro-1H-
2-benzazepine-4-acetic acid;
25 (±)-8-[3-(2-pyridylamino)-1-propyloxy]-2-methyl-3-oxo-2,3,4,5-tetrahydro-1H-2-
benzazepine-4-acetic acid;
(±)-8-[3-(2-imidazolylamino)-1-propyloxy]-3-oxo-2,3,4,5-tetrahydro-1H-2-
benzazepine-4-acetic acid;
(±)-8-[3-[2-(1,4,5,6-tetrahydropyrimidinyl)amino]-1-propyloxy]-3-oxo-2,3,4,5-
30 tetrahydro-1H-2-benzazepine-4-acetic acid;
(±)-8-[3-(6-amino-2-pyridylamino)-1-propyloxy]-3-oxo-2,3,4,5-tetrahydro-1H-2-
benzazepine-4-acetic acid;
(±)-8-[2-(2-benzimidazolyl)ethoxy]-3-oxo-2,3,4,5-tetrahydro-1H-2-benzazepine-4-
acetic acid;

- (±)-8-[2-(4-aza-2-benzimidazolyl)ethoxy]-3-oxo-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetic acid;
- (±)-8-[2-[6-(methylamino)pyridin-2-yl]-1-ethoxy]-3-oxo-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetic acid;
- 5 (±)-8-[2-(benzimidazol-2-yl)-1-ethoxy]-3-oxo-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetic acid;
- (±)-8-[3-(4-aminopyridin-2-ylamino)-1-propyloxy]-2-methyl-3-oxo-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetic acid;
- (±)-3-oxo-8-[3-(pyrimidin-2-ylamino)-1-propyloxy]-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetic acid;
- 10 (R)-8-[3-(4-aminopyridin-2-ylamino)-1-propyloxy]-3-oxo-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetic acid;
- (±)-3-oxo-8-[3-[(1,4,5,6-tetrahydropyrimidin-2-yl)amino]-1-propyloxy]-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetic acid;
- 15 (S)-8-[3-(4-aminopyridin-2-ylamino)-1-propyloxy]-3-oxo-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetic acid;
- (±)-3-oxo-8-[3-[N-(pyridin-2-yl)-N-(*tert*-butoxycarbonyl)amino]-1-propyloxy]-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetic acid;
- (±)-8-[3-[N-(1-oxopyridin-2-yl)-N-(*tert*-butoxycarbonyl)amino]-1-propyloxy]-3-oxo-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetic acid;
- 20 (±)-3-oxo-8-[3-[N-(pyridin-2-yl)-N-(*tert*-butoxycarbonyl)amino]-1-propyloxy]-2-(4-trifluoromethylbenzyl)-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetic acid;
- (±)-3-oxo-8-[3-(pyridin-2-ylamino)-1-propyloxy]-2-(4-trifluoromethylbenzyl)-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetic acid;
- 25 (±)-2-methyl-3-oxo-8-[3-[N-(pyridin-2-yl)-N-(methylamino)-1-propyloxy]-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetic acid;
- (±)-2-benzyl-3-oxo-8-[3-(pyridin-2-ylamino)-1-propyloxy]-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetic acid;
- (±)-2-(carboxymethyl)-3-oxo-8-[3-(pyridin-2-ylamino)-1-propyloxy]-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetic acid;
- 30 (±)-2-(4-aminobenzyl)-3-oxo-8-[3-(pyridin-2-ylamino)-1-propyloxy]-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetic acid;
- (±)-3-oxo-8-[3-[N-(pyridin-2-yl)-N-(benzoyl)amino]-1-propyloxy]-2-(4-trifluoromethylbenzyl)-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetic acid;
- 35 (±)-8-[3-(2-imidazolin-2-ylamino)-1-propyloxy]-2-methyl-3-oxo-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetic acid;

- (±)-3-oxo-8-[3-(pyridin-2-ylamino)-1-propyloxy]-2-(2,2,2-trifluoroethyl)-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetic acid;
- (±)-8-[2-(2-aminothiazol-4-yl)-1-ethoxy]-2-methyl-3-oxo-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetic acid;
- 5 (±)-8-[3-(4,6-dimethylpyridin-2-ylamino)-1-propyloxy]-2-methyl-3-oxo-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetic acid;
- (±)-8-[3-(4,5,6,7-tetrahydro-1H-1,3-diazepin-2-ylamino)-1-propyloxy]-2-methyl-3-oxo-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetic acid;
- (±)-3-oxo-8-[3-[N-(pyridin-2-yl)-N-(*tert*-butylacetyl)amino]-1-propyloxy]-2-(4-trifluoromethylbenzyl)-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetic acid;
- 10 (±)-3-oxo-8-[3-[N-(pyridin-2-yl)-N-(isobutoxycarbonyl)amino]-1-propyloxy]-2-(4-trifluoromethylbenzyl)-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetic acid;
- (S)-3-oxo-8-[3-(pyridin-2-ylamino)-1-propyloxy]-2-(4-trifluoromethylbenzyl)-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetic acid;
- 15 (±)-3-oxo-8-[3-(4-methylpyridin-2-ylamino)-1-propyloxy]-2-(2,2,2-trifluoroethyl)-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetic acid;
- (±)-3-oxo-8-[3-[N-(pyridin-2-yl)-N-(methyl)amino]-1-propyloxy]-2-[4-(trifluoromethyl)benzyl]-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetic acid;
- (S)-3-oxo-8-[3-(pyridin-2-ylamino)-1-propyloxy]-2-(2,2,2-trifluoroethyl)-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetic acid;
- 20 (R)-3-oxo-8-[3-(pyridin-2-ylamino)-1-propyloxy]-2-(2,2,2-trifluoroethyl)-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetic acid;
- (S)-8-[3-(4-methylpyridin-2-ylamino)-1-propyloxy]-3-oxo-2-(2,2,2-trifluoroethyl)-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetic acid;
- 25 (S)-3-oxo-8-[3-(1,4,5,6-tetrahydropyrimidin-2-ylamino)-1-propyloxy]-2-[4-(trifluoromethyl)benzyl]-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetic acid;
- (S)-3-oxo-2-(2-phenylethyl)-8-[3-(pyridin-2-ylamino)-1-propyloxy]-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetic acid;
- (S)-8-[2-[6-(methylamino)pyridin-2-yl]-1-ethoxy]-3-oxo-2-(2-phenylethyl)-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetic acid;
- 30 (S)-8-[2-[6-(methylamino)pyridin-2-yl]-1-ethoxy]-3-oxo-2-(2,2,2-trifluoroethyl)-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetic acid; or
- (S)-8-[2-[6-(methylamino)pyridin-2-yl]-1-ethoxy]-3-oxo-2-[4-(trifluoromethyl)benzyl]-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetic acid;
- 35 or a pharmaceutically acceptable salt thereof.

19. A compound according to claim 1 which is (S)-3-oxo-8-[3-(pyridin-2-ylamino)-1-propyloxy]-2-(2,2,2-trifluoroethyl)-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetic acid or a pharmaceutically acceptable salt thereof.
- 5 20. A compound according to claim 1 which is (S)-8-[2-[6-(methylamino)pyridin-2-yl]-1-ethoxy]-3-oxo-2-(2,2,2-trifluoroethyl)-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetic acid or a pharmaceutically acceptable salt thereof.
- 10 21. A compound according to claim 1 which is (S)-8-[3-(4-methylpyridin-2-ylamino)-1-propyloxy]-3-oxo-2-(2,2,2-trifluoroethyl)-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetic acid or a pharmaceutically acceptable salt thereof.
22. A pharmaceutical composition which comprises a compound according to claim 1 and a pharmaceutically acceptable carrier.
- 15 23. A pharmaceutical composition which comprises a compound according to claim 1, an antineoplastic agent and a pharmaceutically acceptable carrier.
24. The pharmaceutical composition according to claim 23 wherein the
20 antineoplastic agent is topotecan.
25. The pharmaceutical composition according to claim 23 wherein the antineoplastic agent is cisplatin.
- 25 26. A pharmaceutical composition which comprises a compound according to claim 1, an inhibitor of bone resorption and a pharmaceutically acceptable carrier.
27. A method of treating a disease state in which antagonism of the $\alpha_v\beta_3$ receptor is indicated which comprises administering to a subject in need thereof a
30 compound according to claim 1.
28. A method of treating a disease state in which antagonism of the $\alpha_v\beta_5$ receptor is indicated which comprises administering to a subject in need thereof a compound according to claim 1.
- 35 29. A method of treating osteoporosis which comprises administering to a subject in need thereof a compound according to claim 1.

30. A method for inhibiting angiogenesis which comprises administering to a subject in need thereof a compound according to claim 1.

5 31. A method for inhibiting tumor growth or tumor metastasis which comprises administering to a subject in need thereof a compound according to claim 1.

32. A method of treating atherosclerosis or restenosis which comprises administering to a subject in need thereof a compound according to claim 1.

10

33. A method of treating inflammation which comprises administering to a subject in need thereof a compound according to claim 1.

34. A method of inhibiting tumor growth which comprises administering
15 stepwise or in physical combination a compound according to claim 1 and an antineoplastic agent.

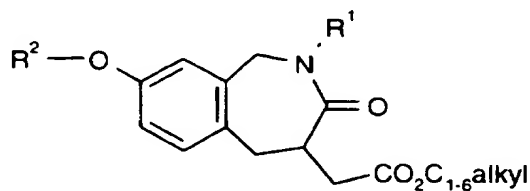
35. The method according to claim 34 wherein the antineoplastic agent is topotecan.

20

36. The method according to claim 34 wherein the antineoplastic agent is cisplatin.

37. A method of treating osteoporosis or inhibiting bone loss which comprises
25 administering stepwise or in physical combination a compound according to claim 1 and an inhibitor of bone resorption.

38. A compound according to formula (II):



30

(II)

wherein:

R^1 is R^7 , or A-C₀₋₄alkyl, A-C₂₋₄alkenyl, A-C₂₋₄alkynyl, A-C₃₋₄oxoalkenyl, A-C₃₋₄oxoalkynyl, A-C₁₋₄aminoalkyl, A-C₃₋₄aminoalkenyl, A-C₃₋₄aminoalkynyl, optionally substituted by any accessible combination of one or more of R^{10} or R^7 ;

A is H, C₃₋₆cycloalkyl, Het or Ar;

- 5 R^7 is -COR⁸, -COCR'₂R⁹, -C(S)R⁸, -S(O)_mOR', -S(O)_mNR'R'', -PO(OR'), -PO(OR')₂, -NO₂, or tetrazolyl;

each R^8 independently is -OR', -NR'R'', -NR'SO₂R', -NR'OR', or -OCR'₂CO(O)R';

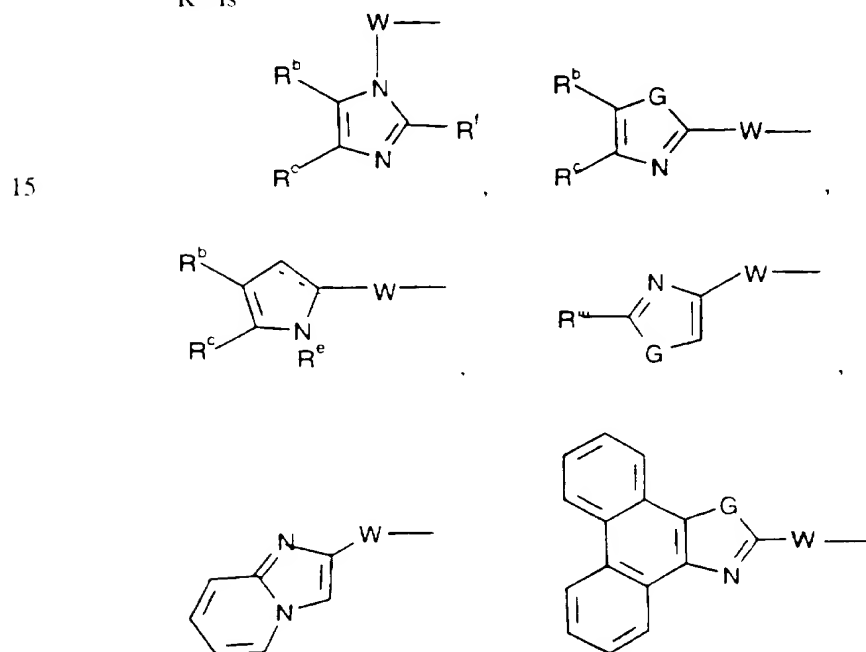
R^9 is -OR', -CN, -S(O)_rR', -S(O)_mNR'₂, -C(O)R', C(O)NR'₂, or -CO₂R';

R^{10} is H, halo, -OR¹¹, -CN, -NR'R¹¹, -NO₂, -CF₃, CF₃S(O)_r-, -CO₂R', -CONR'₂,

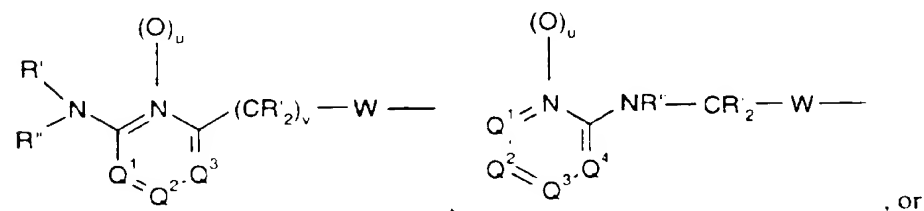
- 10 A-C₀₋₆alkyl-, A-C₁₋₆oxoalkyl-, A-C₂₋₆alkenyl-, A-C₂₋₆alkynyl-, A-C₀₋₆alkyloxy-, A-C₀₋₆alkylamino- or A-C₀₋₆alkyl-S(O)_r-;

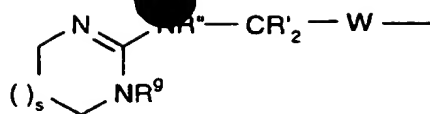
R^{11} is R', -C(O)R', -C(O)NR'₂, -C(O)OR', -S(O)_mR', or -S(O)_mNR'₂;

R^2 is



20





W is $-(\text{CHR}^g)_a\text{-U-}(\text{CHR}^g)_b\text{-}$;

U is absent or CO, CR^g_2 , $\text{C(=CR}^g_2)$, S(O)_k , O, NR^g , CR^gOR^g , $\text{CR}^g(\text{OR}^k)\text{CR}^g_2$,
 5 $\text{CR}^g_2\text{CR}^g(\text{OR}^k)$, C(O)CR^g_2 , $\text{CR}^g_2\text{C(O)}$, CONR^i , NR^iCO , OC(O) , C(O)O , C(S)O , OC(S) ,
 C(S)NR^g , $\text{NR}^g\text{C(S)}$, $\text{S(O)}_2\text{NR}^g$, $\text{NR}^g\text{S(O)}_2$, N=N , NR^gNR^g , NR^gCR^g_2 , CR^g_2NR^g , CR^g_2O ,
 OCR^g_2 , $\text{C}\equiv\text{C}$ or $\text{CR}^g=\text{CR}^g$;

G is NR^e , S or O;

R^g is H, C_{1-6} alkyl, Het- C_{0-6} alkyl, C_{3-7} cycloalkyl- C_{0-6} alkyl or Ar- C_{0-6} alkyl;

10 R^k is R^g , $-\text{C(O)R}^g$, or $-\text{C(O)OR}^f$;

R^i is H, C_{1-6} alkyl, Het- C_{0-6} alkyl, C_{3-7} cycloalkyl- C_{0-6} alkyl, Ar- C_{0-6} alkyl, or
 C_{1-6} alkyl substituted by one to three groups chosen from halogen, CN, NR^g_2 , OR^g , SR^g ,
 CO_2R^g , and $\text{CON(R}^g)_2$;

R^f is H, C_{1-6} alkyl or Ar- C_{0-6} alkyl;

15 R^e is H, C_{1-6} alkyl, Ar- C_{0-6} alkyl, Het- C_{0-6} alkyl, C_{3-7} cycloalkyl- C_{0-6} alkyl, or
 $(\text{CH}_2)_k\text{CO}_2\text{R}^g$;

R^b and R^c are independently selected from H, C_{1-6} alkyl, Ar- C_{0-6} alkyl, Het- C_{0-6}
 alkyl , or C_{3-6} cycloalkyl- C_{0-6} alkyl, halogen, CF_3 , OR^f , $\text{S(O)}_k\text{R}^f$, COR^f , NO_2 , $\text{N(R}^f)_2$,
 $\text{CO(NR}^f)_2$, $\text{CH}_2\text{N(R}^f)_2$, or R^b and R^c are joined together to form a five or six membered
 20 aromatic or non-aromatic carbocyclic or heterocyclic ring, optionally substituted by up to
 three substituents chosen from halogen, CF_3 , C_{1-4} alkyl, OR^f , $\text{S(O)}_k\text{R}^f$, COR^f , CO_2R^f , OH,
 NO_2 , $\text{N(R}^f)_2$, $\text{CO(NR}^f)_2$, and $\text{CH}_2\text{N(R}^f)_2$; or methylenedioxy;

Q^1 , Q^2 , Q^3 and Q^4 are independently N or C-R^y , provided that no more than one of
 Q^1 , Q^2 , Q^3 and Q^4 is N;

25 R^j is H, C_{1-6} alkyl, Ar- C_{0-6} alkyl or C_{3-6} cycloalkyl- C_{0-6} alkyl;

R'' is R^j , $-\text{C(O)R}^j$ or $-\text{C(O)OR}^j$;

R''' is H, C_{1-6} alkyl, Ar- C_{0-6} alkyl, Het- C_{0-6} alkyl, or C_{3-6} cycloalkyl- C_{0-6} alkyl,
 halogen, CF_3 , OR^f , $\text{S(O)}_k\text{R}^f$, COR^f , NO_2 , $\text{N(R}^f)_2$, $\text{CO(NR}^f)_2$, $\text{CH}_2\text{N(R}^f)_2$;

R^y is H, halo, $-\text{OR}^g$, $-\text{SR}^g$, $-\text{CN}$, $-\text{NR}^g\text{R}^k$, $-\text{NO}_2$, $-\text{CF}_3$, $\text{CF}_3\text{S(O)}_r$, $-\text{CO}_2\text{R}^g$, $-\text{COR}^g$
 30 or $-\text{CONR}^g_2$, or C_{1-6} alkyl optionally substituted by halo, $-\text{OR}^g$, $-\text{SR}^g$, $-\text{CN}$, $-\text{NR}^g\text{R}''$, $-\text{NO}_2$,
 $-\text{CF}_3$, $\text{R}^j\text{S(O)}_r$, $-\text{CO}_2\text{R}^g$, $-\text{COR}^g$ or $-\text{CONR}^g_2$;

a is 0, 1 or 2;

b is 0, 1 or 2;

k is 0, 1 or 2;

35 m is 1 or 2;

r is 0, 1 or 2;
 s is 0, 1 or 2;
 u is 0 or 1; and
 v is 0 or 1;

5 or a pharmaceutically acceptable salt thereof.

39. A compound according to claim 38 which is:

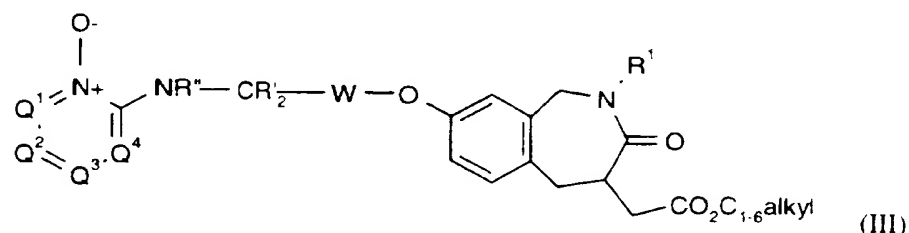
methyl (±)-3-oxo-8-[3-(pyridin-2-ylamino)-1-propyloxy]-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetate; or

10 ethyl (±)-8-[3-(4-aminopyridin-2-ylamino)-1-propyloxy]-3-oxo-2,3,4,5-tetrahydro-1H-2-benzazepine-4-acetate;

or a pharmaceutically acceptable salt thereof.

40. A compound according to formula (III):

15



R¹ is R⁷, or A-C₀₋₄alkyl, A-C₂₋₄alkenyl, A-C₂₋₄alkynyl, A-C₃₋₄oxoalkenyl, A-C₃₋₄oxoalkynyl, A-C₁₋₄aminoalkyl, A-C₃₋₄aminoalkenyl, A-C₃₋₄aminoalkynyl, optionally substituted by any accessible combination of one or more of R¹⁰ or R⁷;

20 A is H, C₃₋₆cycloalkyl, Het or Ar;

R⁷ is -COR⁸, -COCR²R⁹, -C(S)R⁸, -S(O)_mOR', -S(O)_mNR'R'', -PO(OR'), -PO(OR')₂, -NO₂, or tetrazolyl;

each R⁸ independently is -OR', -NR'R'', -NR'SO₂R', -NR'OR', or -OCR²CO(O)R';

25 R⁹ is -OR', -CN, -S(O)_rR', -S(O)_mNR'₂, -C(O)R', C(O)NR'₂, or -CO₂R';

R¹⁰ is H, halo, -OR¹¹, -CN, -NR'R¹¹, -NO₂, -CF₃, CF₃S(O)_r, -CO₂R', -CONR'₂, A-C₀₋₆alkyl-, A-C₁₋₆oxoalkyl-, A-C₂₋₆alkenyl-, A-C₂₋₆alkynyl-, A-C₀₋₆alkyloxy-, A-C₀₋₆alkylamino- or A-C₀₋₆alkyl-S(O)_r;

R¹¹ is R', -C(O)R', -C(O)NR'₂, -C(O)OR', -S(O)_mR', or -S(O)_mNR'₂;

30 W is -(CHR^g)_a-U-(CHR^g)_b-;

U is absent or CO, CR^g₂, C(=CR^g₂), S(O)_k, O, NR^g, CR^gOR^g, CR^g(OR^k)CR^g₂, CR^g₂CR^g(OR^k), C(O)CR^g₂, CR^g₂C(O), CONR^l, NR^lCO, OC(O), C(O)O, C(S)O, OC(S),

$C(S)NR^g$, $NR^gC(S)$, $S(O)_2NR^g$, $NR^gS(O)_2$, $N=N$, NR^gNR^g , $NR^gCR^g_2$, $CR^g_2NR^g$, CR^g_2O , OCR^g_2 , $C\equiv C$ or $CR^g=CR^g$;

R^g is H, C_{1-6} alkyl, Het- C_{0-6} alkyl, C_{3-7} cycloalkyl- C_{0-6} alkyl or Ar- C_{0-6} alkyl;

R^k is R^g , $-C(O)R^g$, or $-C(O)OR^f$;

- 5 R^i is H, C_{1-6} alkyl, Het- C_{0-6} alkyl, C_{3-7} cycloalkyl- C_{0-6} alkyl, Ar- C_{0-6} alkyl, or C_{1-6} alkyl substituted by one to three groups chosen from halogen, CN, NR^g_2 , OR^g , SR^g , CO_2R^g , and $CON(R^g)_2$;

R^f is H, C_{1-6} alkyl or Ar- C_{0-6} alkyl;

Q^1 , Q^2 , Q^3 and Q^4 are independently N or C- R^y , provided that no more than one of

- 10 Q^1 , Q^2 , Q^3 and Q^4 is N;

R' is H, C_{1-6} alkyl, Ar- C_{0-6} alkyl or C_{3-6} cycloalkyl- C_{0-6} alkyl;

R'' is R' , $-C(O)R'$ or $-C(O)OR'$;

R^y is H, halo, $-OR^g$, $-SR^g$, $-CN$, $-NR^gR^k$, $-NO_2$, $-CF_3$, $CF_3S(O)_r$, $-CO_2R^g$, $-COR^g$ or $-CONR^g_2$, or C_{1-6} alkyl optionally substituted by halo, $-OR^g$, $-SR^g$, $-CN$, $-NR^gR''$, $-NO_2$,

- 15 $-CF_3$, $R'S(O)_r$, $-CO_2R^g$, $-COR^g$ or $-CONR^g_2$;

a is 0, 1 or 2;

b is 0, 1 or 2;

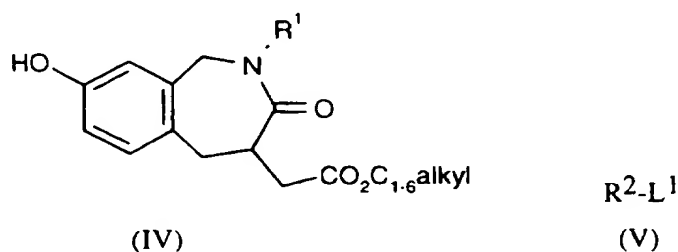
m is 1 or 2; and

r is 0, 1 or 2;

- 20 or a pharmaceutically acceptable salt thereof.

41. A process for preparing a compound of the formula (I) as defined in claim 1, which process comprises reacting a compound of formula (IV) with a compound of formula (V):

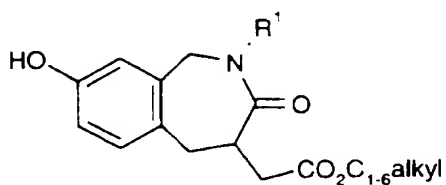
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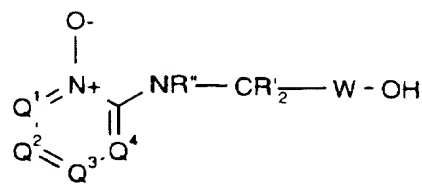
wherein R^1 and R^2 are as defined in formula (I), with any reactive functional groups protected, and L^1 is OH or halo;

- 30 and thereafter removing any protecting groups, and optionally forming a pharmaceutically acceptable salt.

42. A process for preparing a compound of the formula (I) as defined in claim 1, which process comprises reacting a compound of formula (IV) with a compound of formula (VI):



(IV)

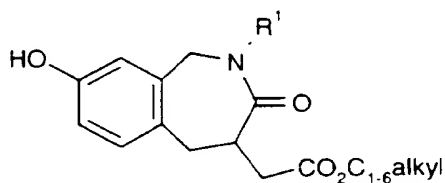


(VI)

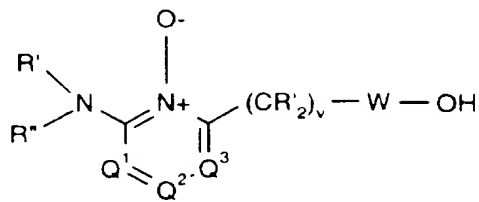
wherein R¹, R', R'', W, Q¹, Q², Q³ and Q⁴ are as defined in formula (I), with any reactive functional groups protected;

and thereafter removing any protecting groups, and optionally forming a pharmaceutically acceptable salt.

43. A process for preparing a compound of the formula (I) as defined in claim 1, which process comprises reacting a compound of formula (IV) with a compound of formula (VII):



(IV)



(VII)

wherein R¹, R', R'', W, Q¹, Q², Q³ and v are as defined in formula (I), with any reactive functional groups protected;

and thereafter removing any protecting groups, and optionally forming a pharmaceutically acceptable salt.

44. A compound according to any one of claims 1 to 21 for use as a medicament.

45. The use of a compound of the formula (I) as defined in claim 1 in the manufacture of a medicament for the treatment of diseases in which antagonism of the α_vβ₃ receptor is indicated.

46. The use of a compound of the formula (I) as defined in claim 1 in the manufacture of a medicament for the treatment of diseases in which antagonism of the $\alpha_v\beta_5$ receptor is indicated.

5

47. The use of a compound of the formula (I) as defined in claim 1 in the manufacture of a medicament for the treatment of osteoporosis.

48. The use of a compound of the formula (I) as defined in claim 1 in the manufacture of a medicament for the inhibition of angiogenesis.

10

49. The use of a compound of the formula (I) as defined in claim 1 in the manufacture of a medicament for the inhibition of tumor growth or tumor metastasis.

15

50. The use of a compound of the formula (I) as defined in claim 1 in the manufacture of a medicament for the treatment of atherosclerosis or restenosis.

51. The use of a compound of the formula (I) as defined in claim 1 in the manufacture of a medicament for the treatment of inflammation.

20

52. The use of a compound of the formula (I) as defined in claim 1 and an antineoplastic agent in the manufacture of a medicament for the inhibition of tumor growth in physical combination or for stepwise administration.

25

53. The use according to claim 52 wherein the antineoplastic agent is topotecan.

54. The use according to claim 52 wherein the antineoplastic agent is cisplatin.

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55. The use of a compound of the formula (I) as defined in claim 1 and an inhibitor of bone resorption in the manufacture of a medicament for the treatment of osteoporosis in physical combination or for stepwise administration.

INTERNATION SEARCH REPORT

International application No.
PCT/US97/18001

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) Please See Extra Sheet.

US CL 514/215, 540/523

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. 514/215; 540/523

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

Please See Extra Sheet.

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 96/00574 A1 (SMITHKLINE BEECHAM CORPORATION) 11	1-45
---	January 1996, see whole article, especially pages 22-23.	-----
Y		1-45
Y	WO 96/26190 A1 (SMITHKLINE BEECHAM CORPORATION) 29	1-45
	August 1996, see whole article.	
Y	WO 96/06087 A1 (SMITHKLINE BEECHAM CORPORATION) 29	1-45
	February 1996, see whole article.	
Y	WO 96/00730 A1 (SMITHKLINE BEECHAM CORPORATION) 11	1-45
	January 1996, see whole article.	

☐ Further documents are listed in the continuation of Box C

☐ See patent family annex.

* Special categories of cited documents	11*	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
11* document defining the general state of the art which is not considered to be of particular relevance	11*	document of particular relevance, the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
11* earlier document published on or after the international filing date	11*	document of particular relevance, the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
11* document which in itself throws doubt on priority claim(s) which is cited to establish the publication date of another citation or other special reason has been cited	11*	document member of the same patent family
11* document referring to an oral disclosure, use, exhibition or other means		
11* document published prior to the international filing date but later than the priority date(s)		

Date of the actual completion of the international search

21 NOVEMBER 1997

Date of mailing of the international search report

29 DEC 1997

Name and mailing address of the ISA/US
Commissioner of Patents and Trademarks
Box PCT
Washington, D.C. 20231

Facsimile No (703) 305-3230

Authorized officer

CELIA CHANG

Telephone No (703) 308-1235

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US97/18001

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

Please See Extra Sheet.

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

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Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
☐ No protest accompanied the payment of additional search fees.

A CLASSIFICATION OF SUBJECT MATTER
IPC (6).

A61K 31/44, 31/47, 31/52, 31/55, 31/415, 31/445, 31/495, C07D 223/16, 233/56, 233/64, 235/18, 235/22, 243/14, 401/12, 401/14, 403/12, 413/12, 417/12, 487/00

B FIELDS SEARCHED

Electronic data bases consulted (Name of data base and where practicable terms used):

CAS-structure

APS-image

Dialog-vitronectin, integrin, osteocalcin, osteoblast, osteoporosis

BOX II OBSERVATIONS WHERE UNITY OF INVENTION WAS LACKING

This ISA found multiple inventions as follows:

This application contains the following inventions or groups of inventions which are not so linked as to form a single inventive concept under PCT Rule 13.1. In order for all inventions to be searched, the appropriate additional search fees must be paid.

Group I, claims 1-45, drawn to compounds, compositions and method of use.

Group II, claim 46, drawn to product for antagonizing $\alpha V\beta 5$ receptor.

Group III, claim 47, drawn to product for treating osteoporosis.

Group IV, claim 48, drawn to product for treating angiogenesis.

Group V, claim 49, drawn to product for inhibiting tumor growth.

Group VI, claim 50, drawn to product for treating atherosclerosis.

Group VII, claim 51, drawn to product for treating inflammation.

Group VIII, claims 52-54, drawn to product containing multiple active ingredients for treating tumor.

Group IX, claim 55, drawn to product containing multiple active ingredients for treating bone resorption.

The inventions listed as Groups I-IX do not relate to a single inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons: compound per se and multiple ingredient products do not share the same technical feature for patentability since compound per se depends on the elements, bonding arrangement and chemical property for activity while a multiple active ingredient composition depends on the specifics of each component and their quantitative relationship for its activity.

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